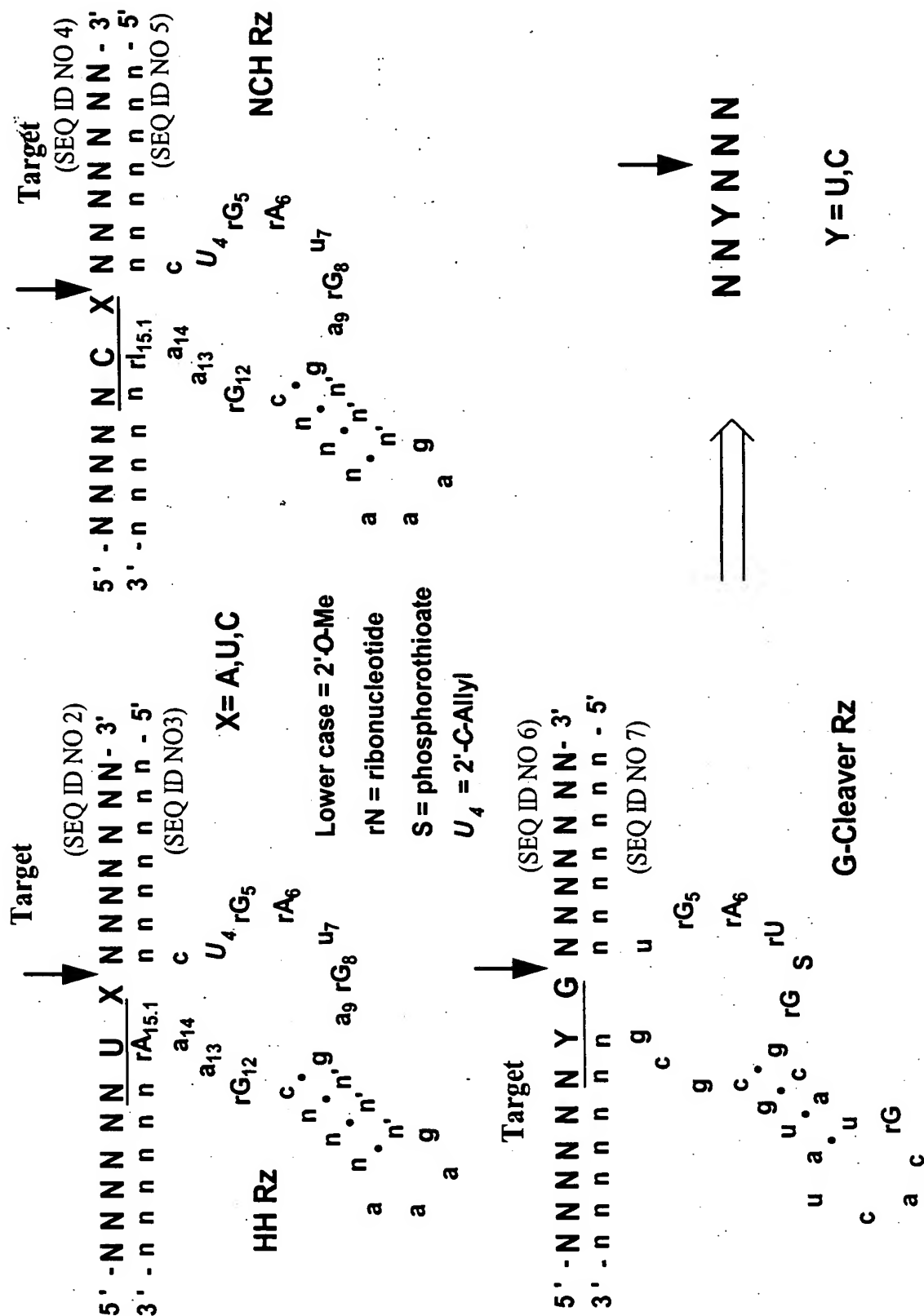
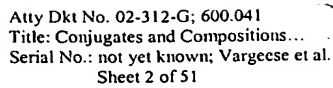
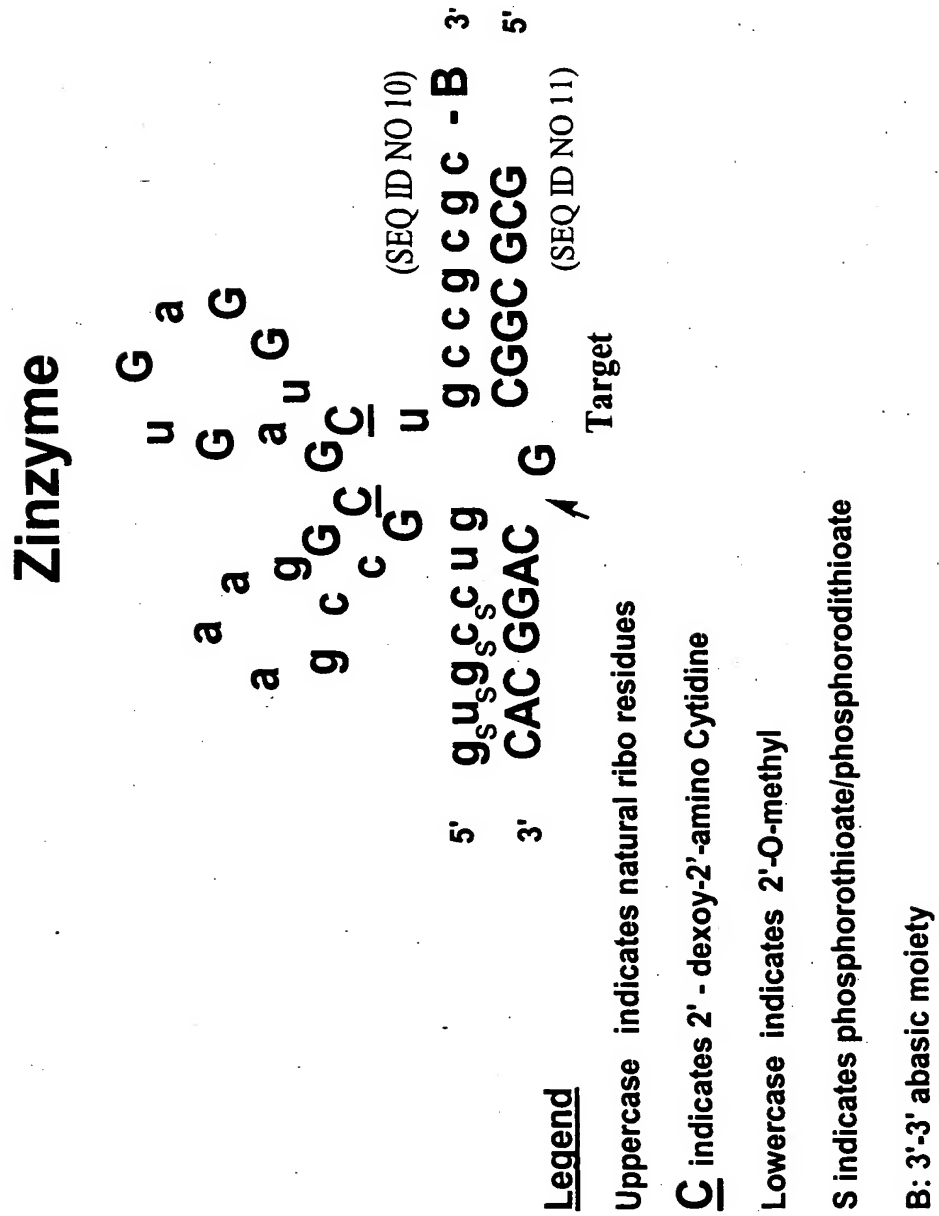


**Figure 1: Examples of Nuclease Stable Ribozyme Motifs**

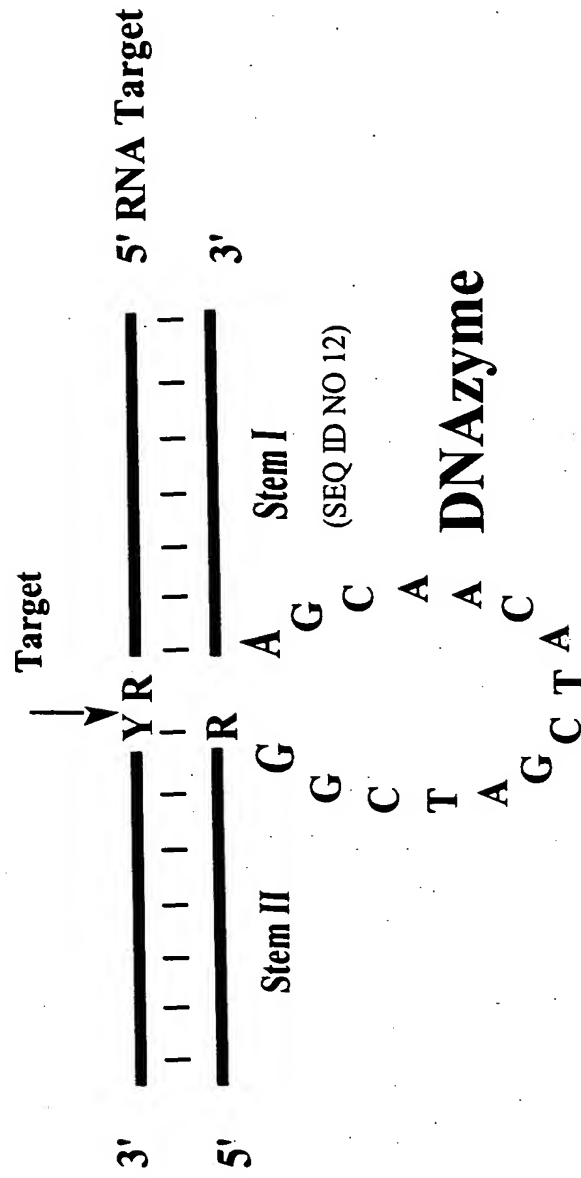




**Figure 3: Stabilized Zinzyme Ribozyme Motif**



**Figure 4: DNAzyme Motif**

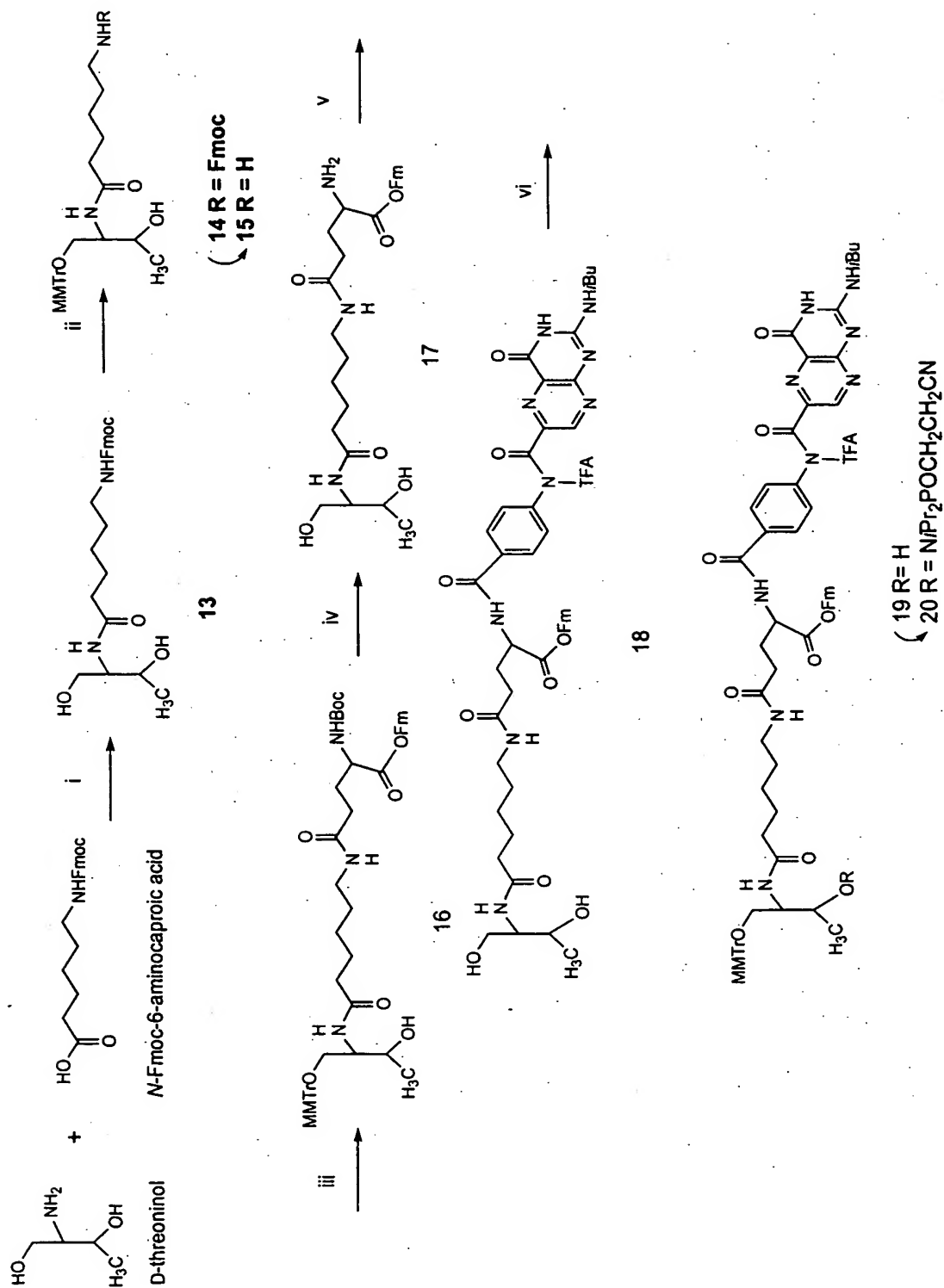


**Legend**

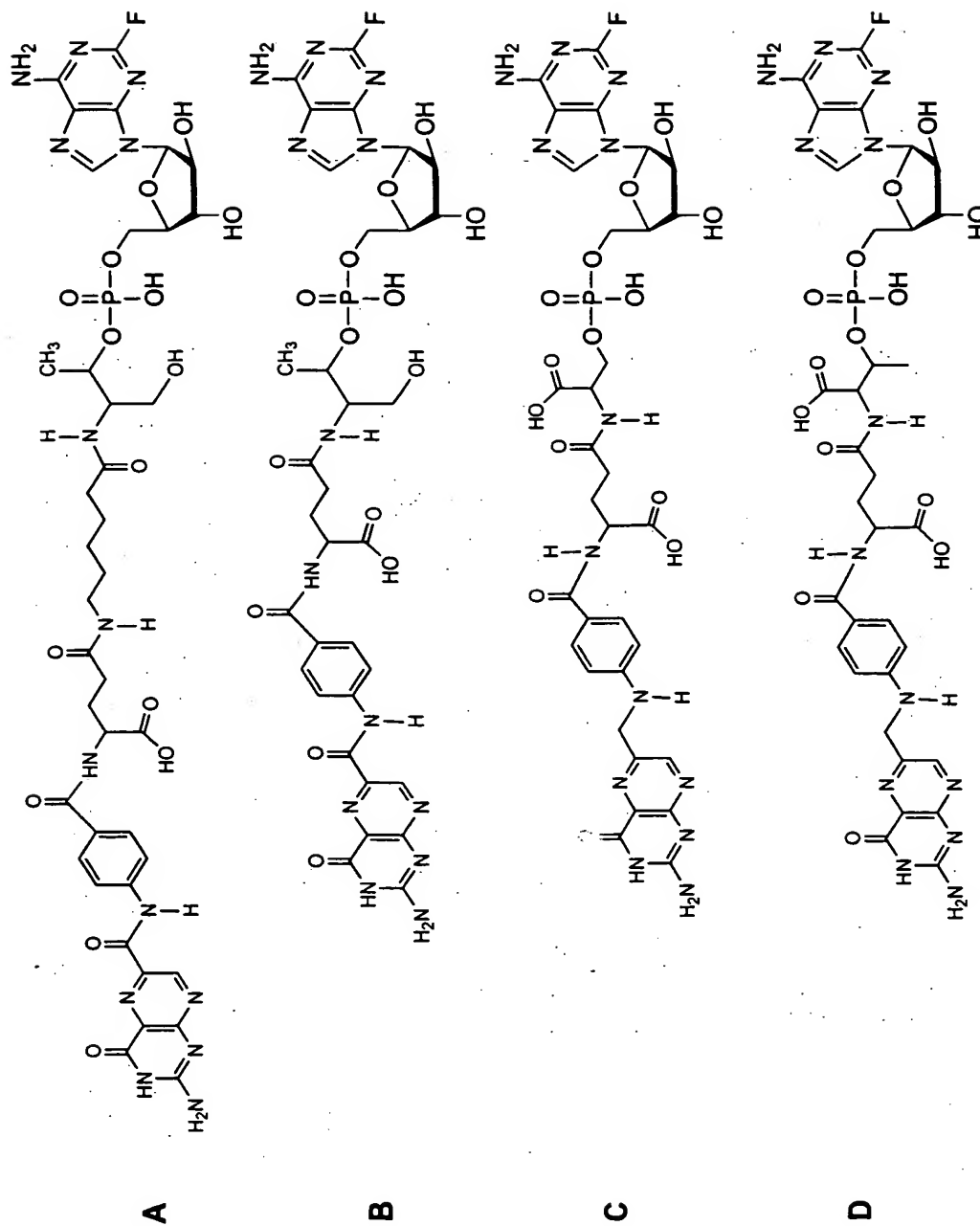
**Y = U or C**

**R = A or G**

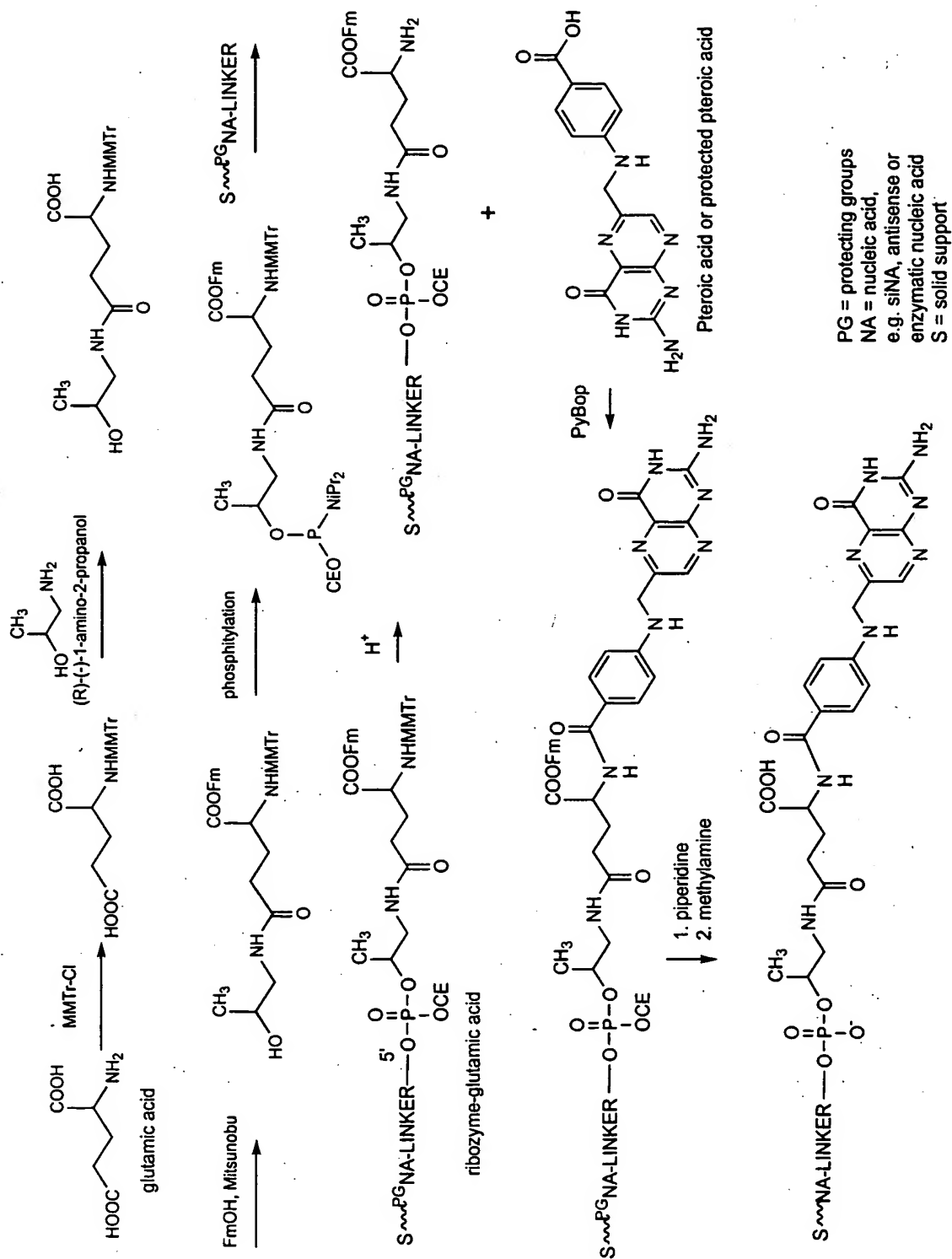
**Figure 5: Synthesis of Folate Linked phosphoramidite**



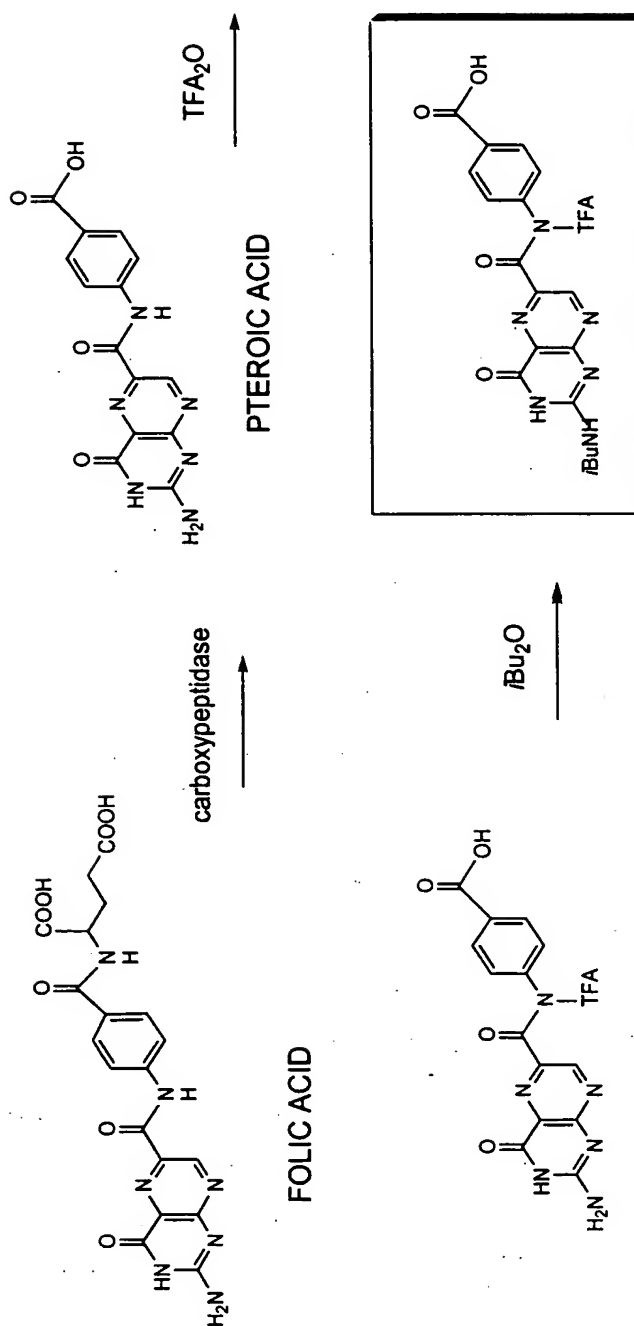
**Figure 6: Fludarabine-Folate conjugates**



**Figure 7: Solid Phase Post-synthetic conjugation of pterotic acid**

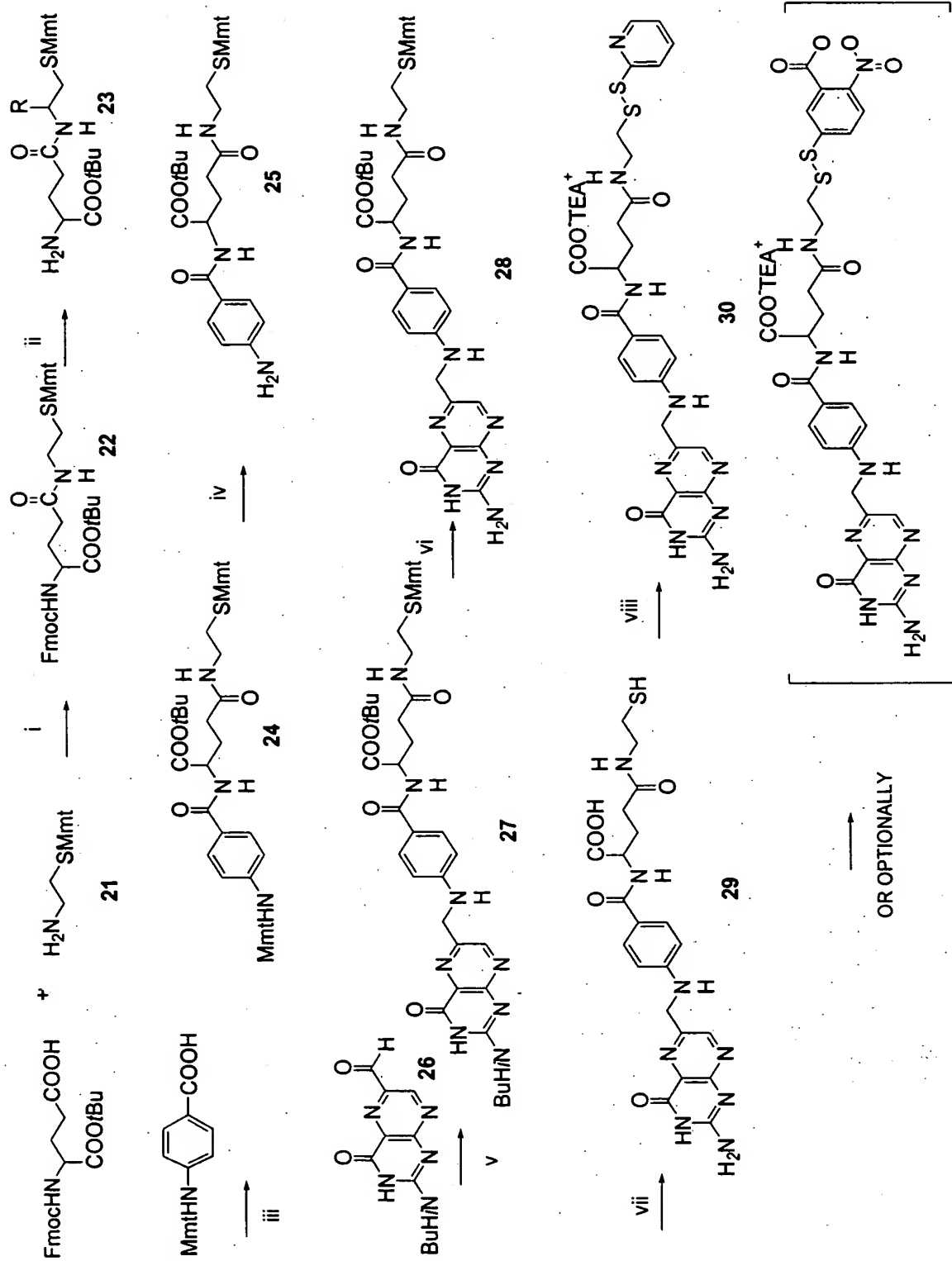


**Figure 8: Chemo-enzymatic synthesis of pteronic acid synthon**

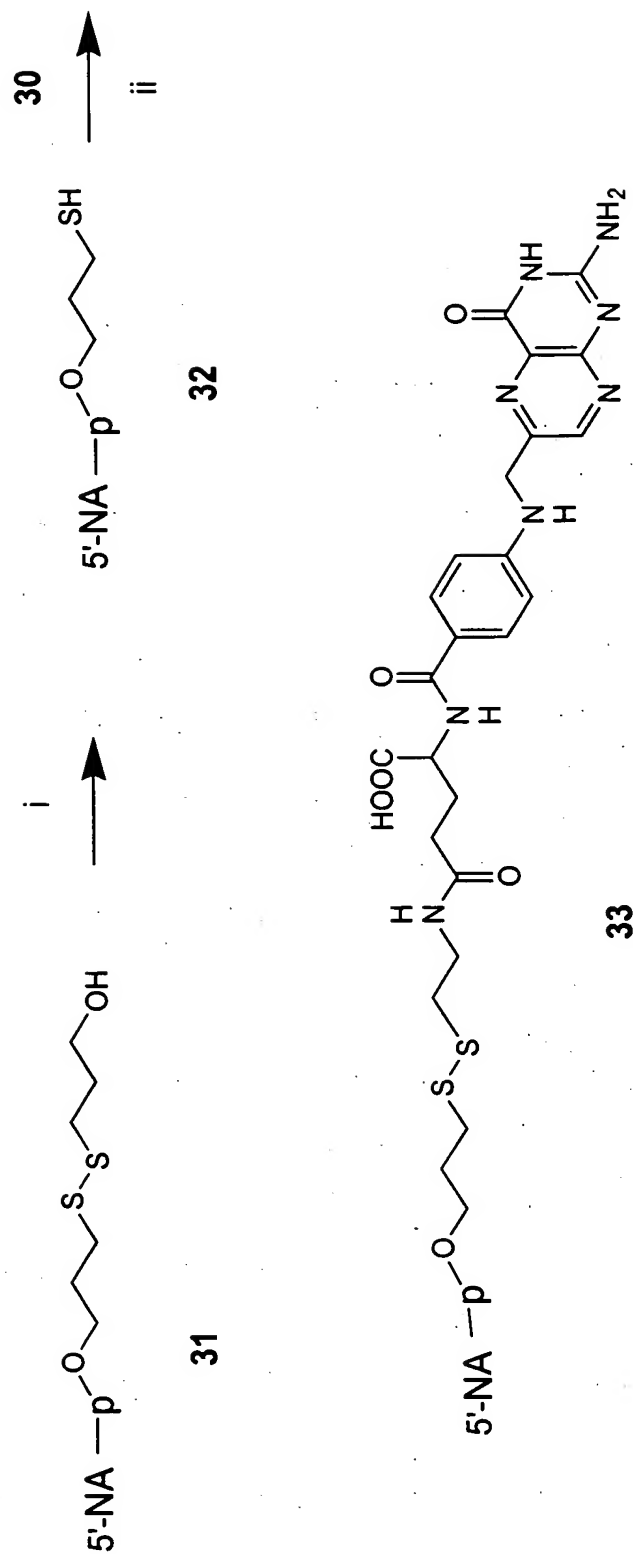




**Figure 9**

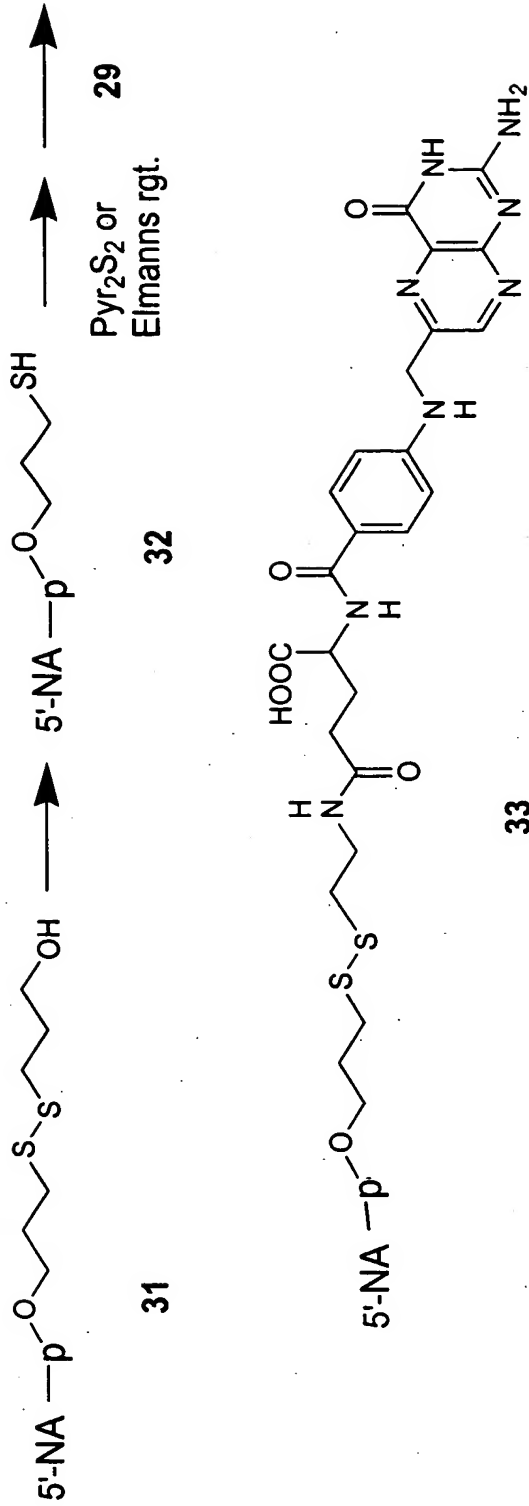


**Figure 10**



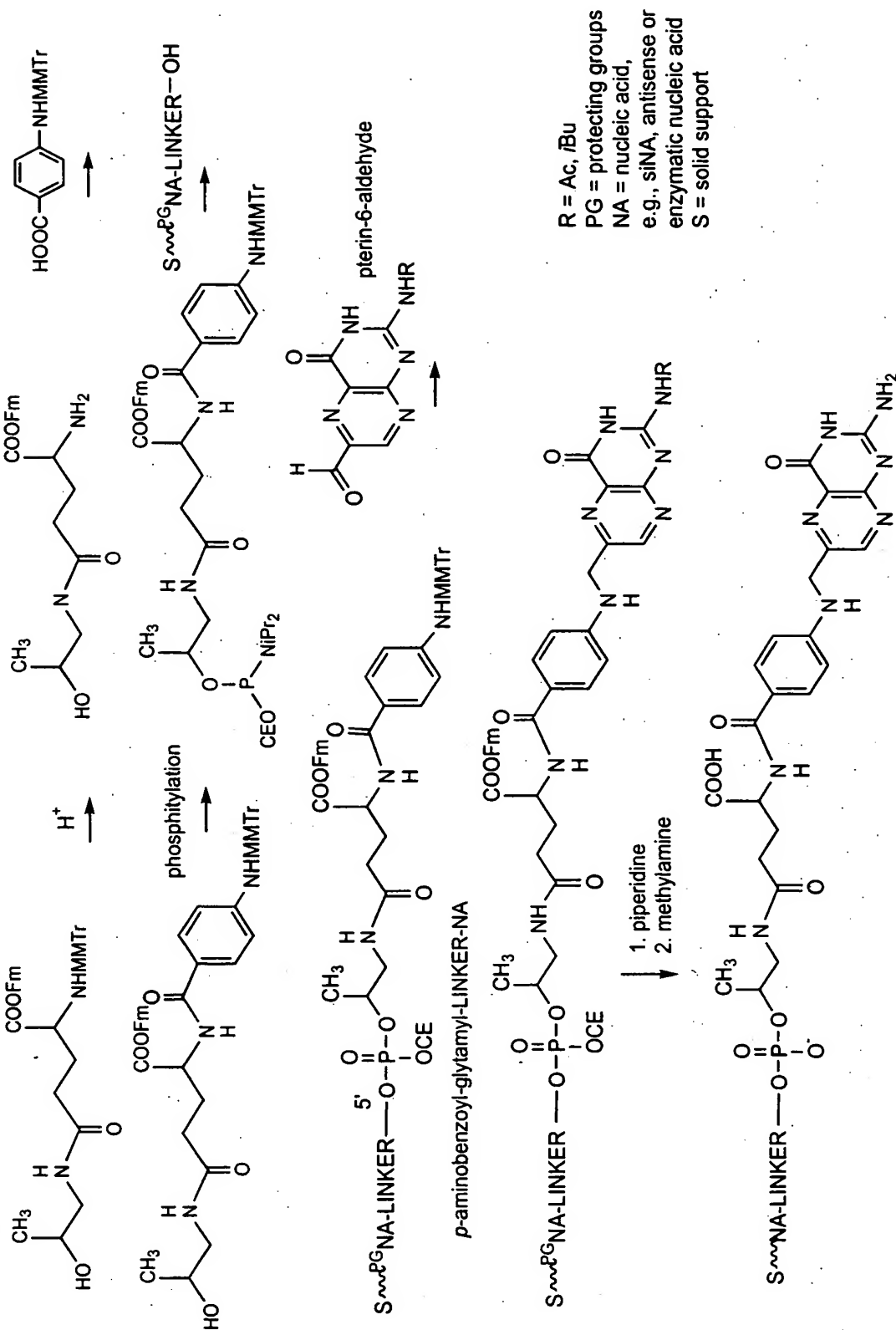
NA = Nucleic Acid, such as siNA, antisense, or enzymatic nucleic acid  
 p = phosphorous moiety

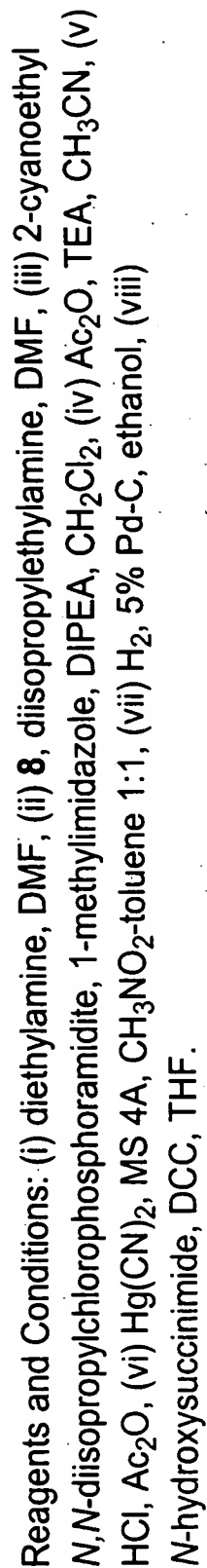
**Figure 11**



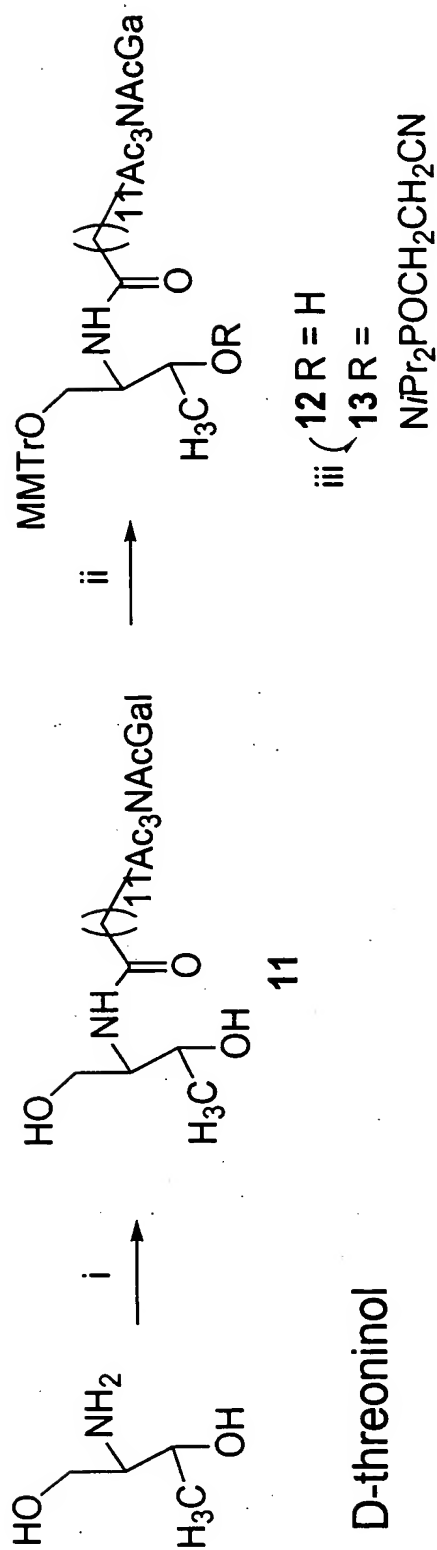
NA = Nucleic Acid, such as siNA, antisense, or enzymatic nucleic acid  
 p = phosphorous moiety

**Figure 12: Solid Phase Post-synthetic conjugation of pterioic acid**



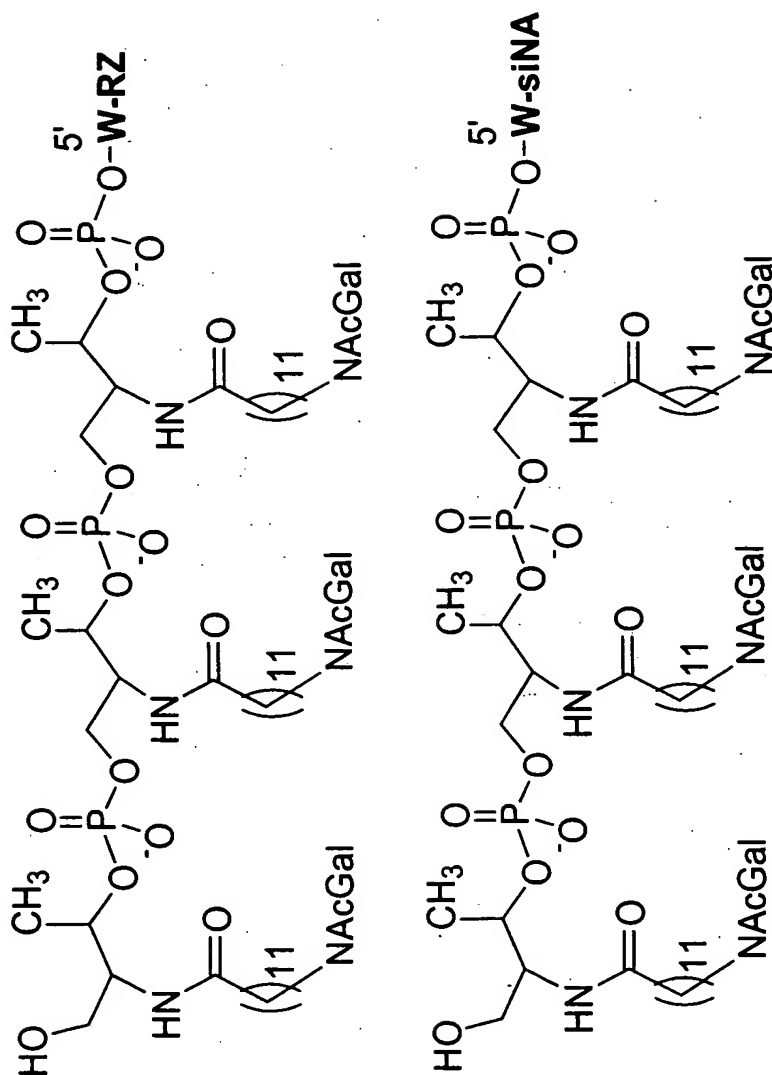


**Figure 14: Synthesis of *N*-acetyl-*D*-galactosamine-*D*-threoninol conjugate**



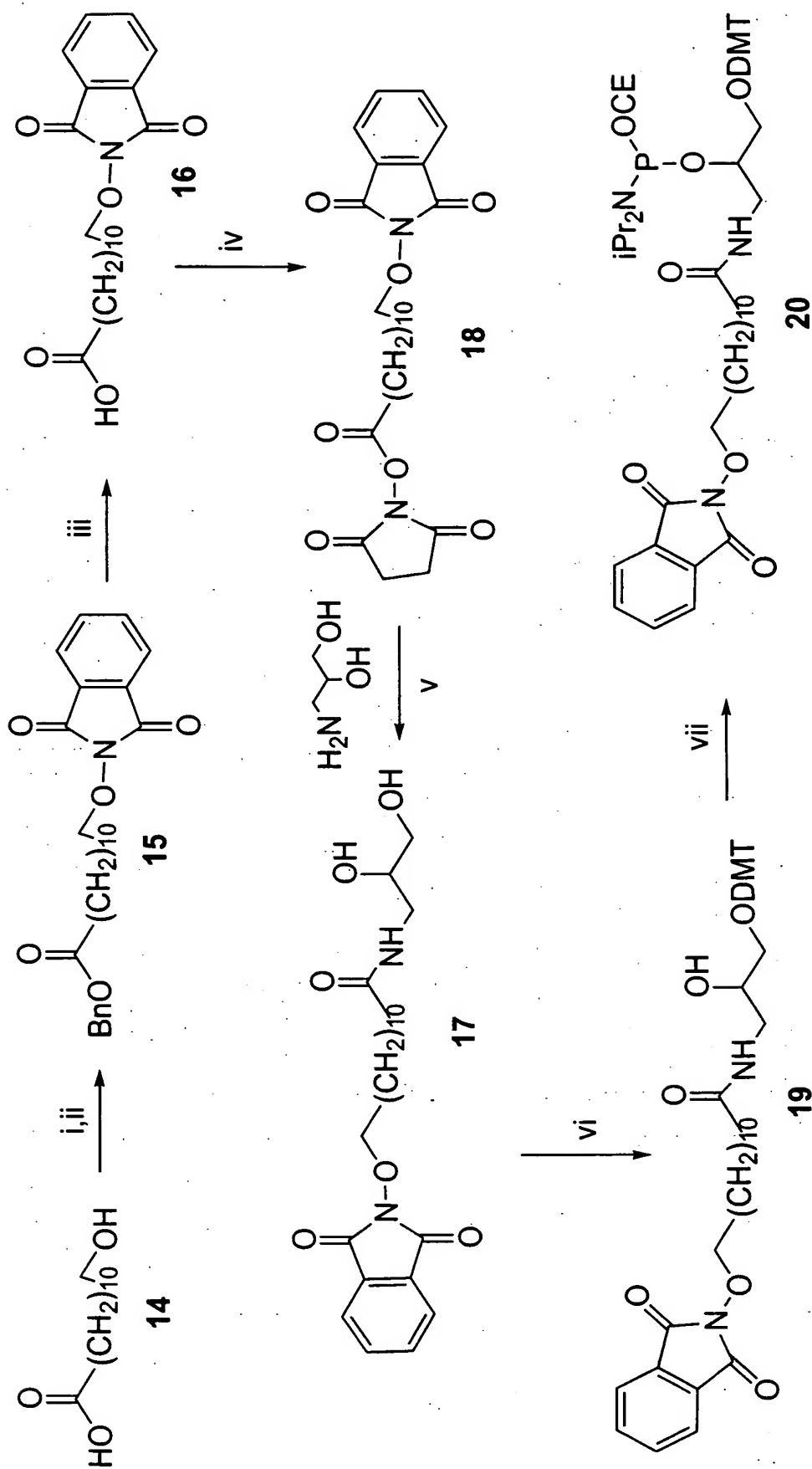
Reagents and Conditions: (i) 7, DCC, *N*-hydroxysuccinimide, (ii) MMTr-Cl, pyridine, (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, 1-methylimidazole, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>.

**Figure 15: Conjugation of targeting ligands to the 5'-end of a Ribozyme or siNA molecule**



**N-acetyl-D-galactosamine conjugate**

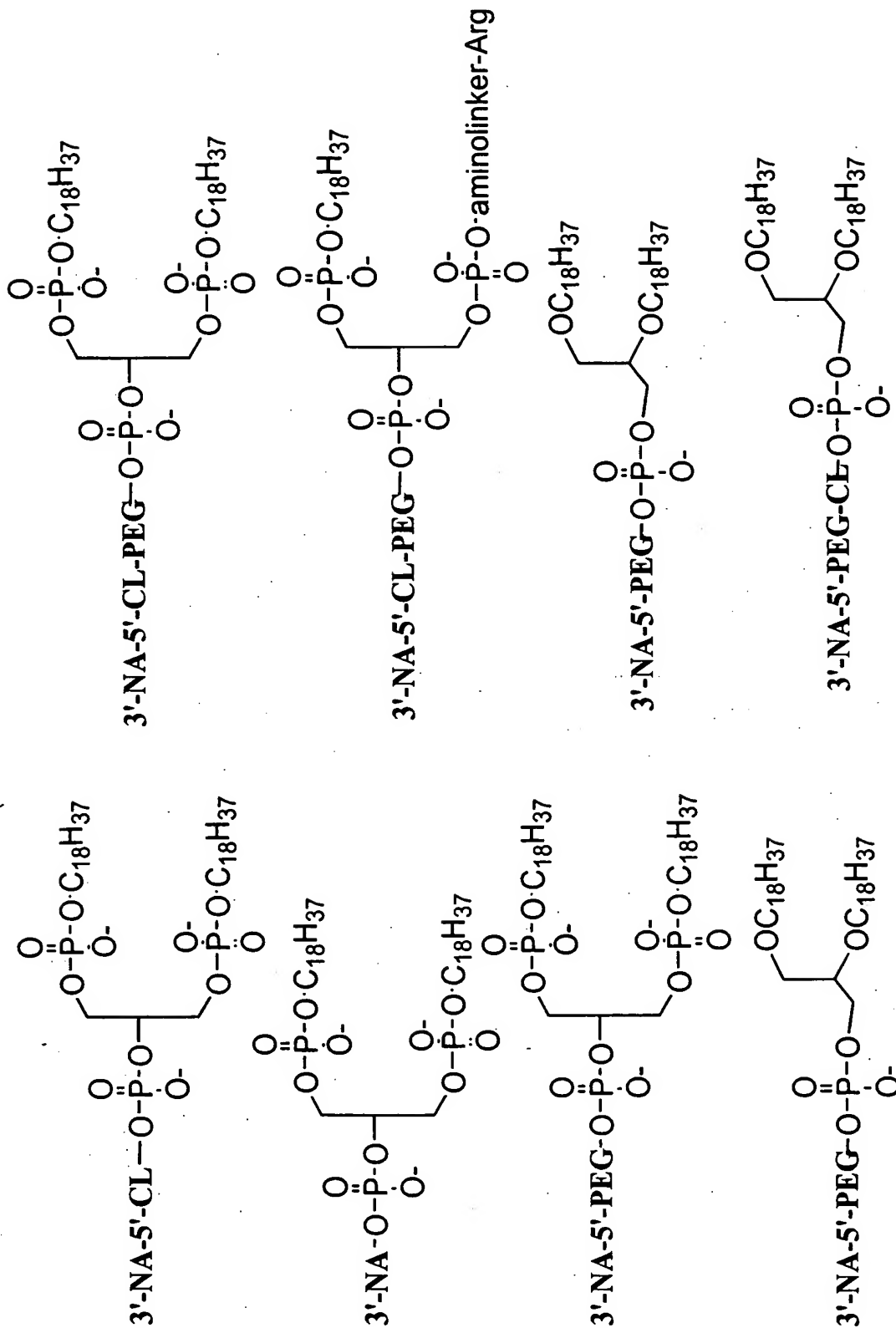
**Figure 16: Synthesis of dodecanoic acid linker**







**Figure 18: Nucleic Acid/Phospholipid Conjugates**



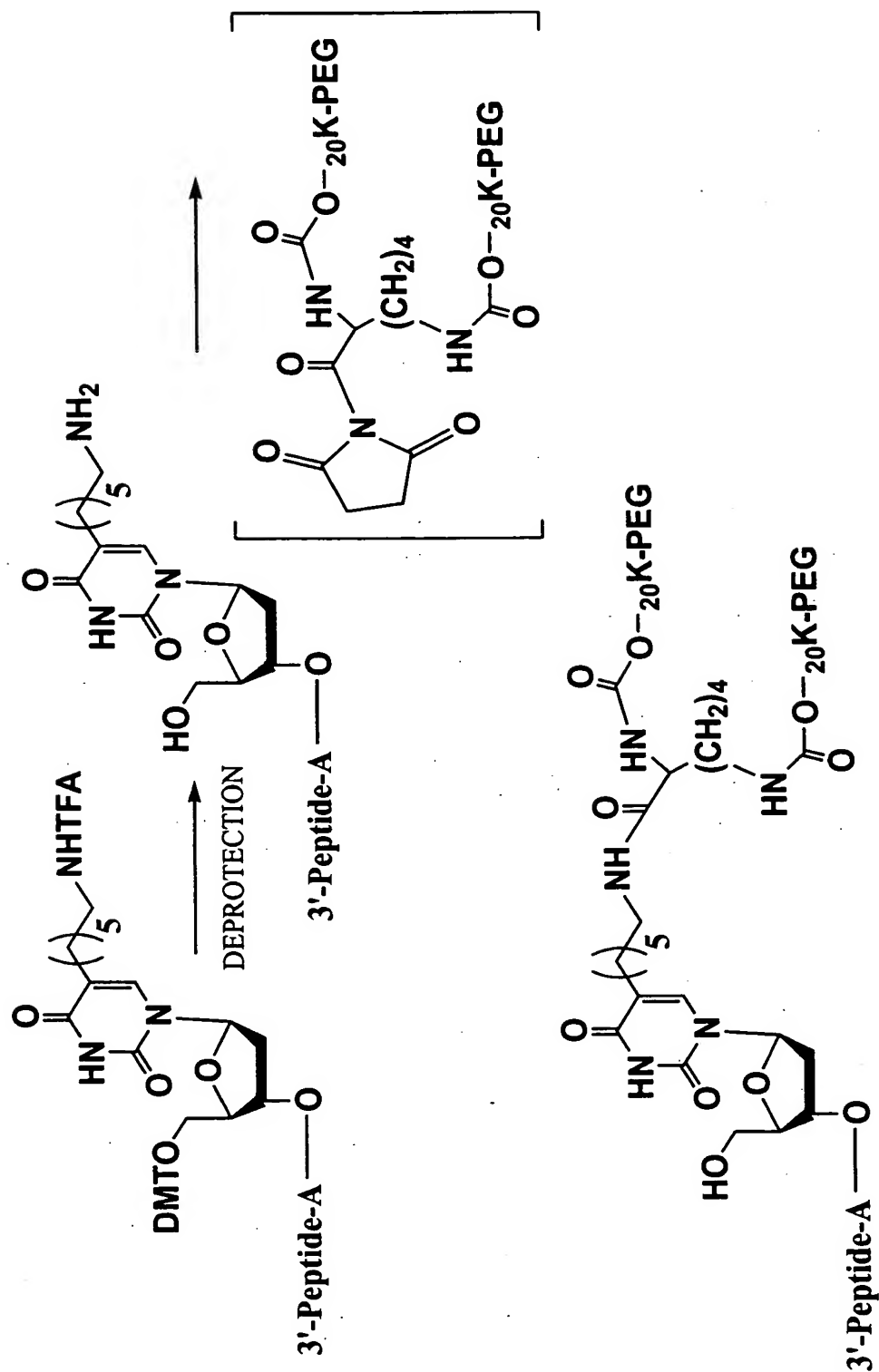
PEG=polyethylene glycol

CL=cleavable linker (e.g. A-dT, C-dT)

NA= Nucleic Acid Molecule such as siNA, antisense, or enzymatic nucleic acid

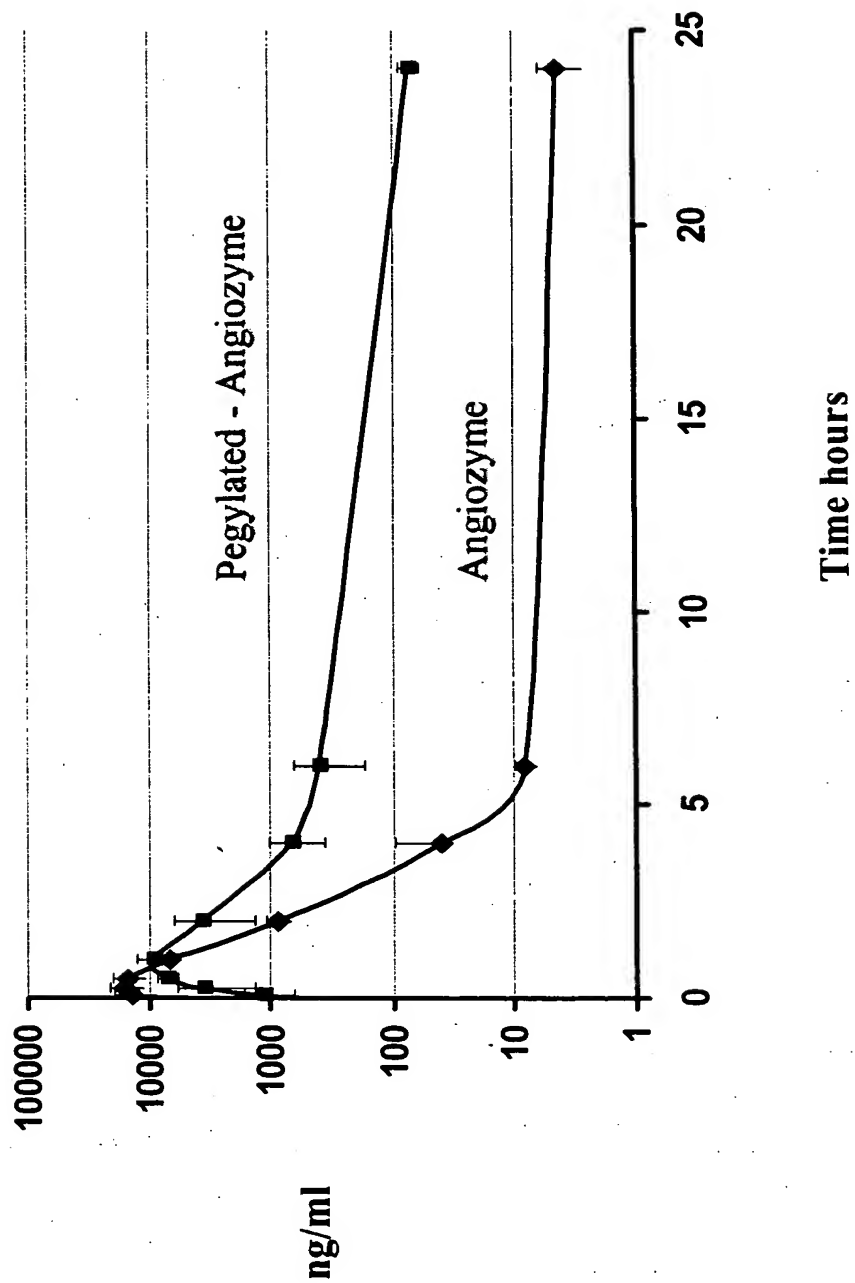


**Figure 20: Peptide PEG Conjugate**

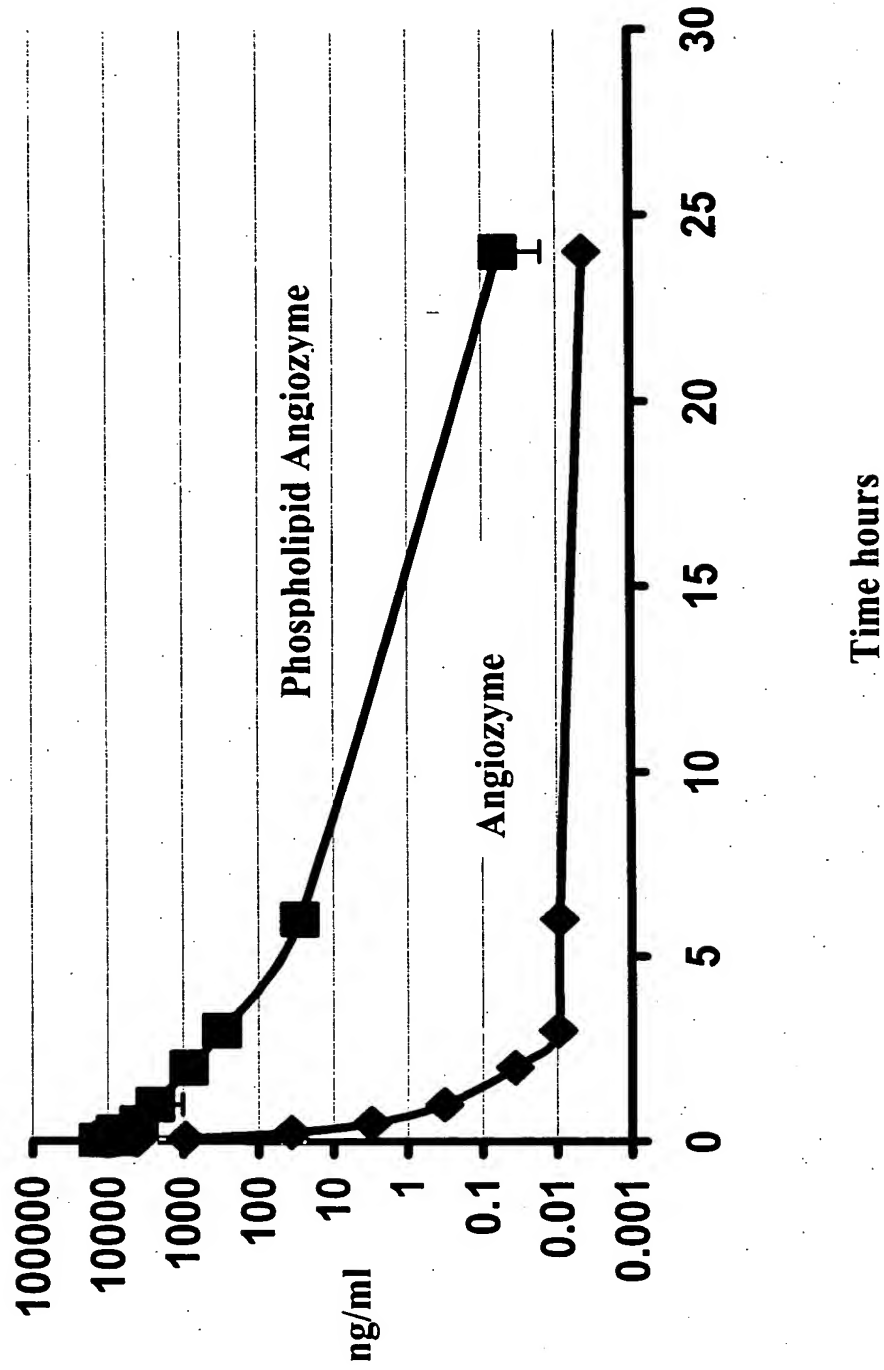


**A = Adenosine**

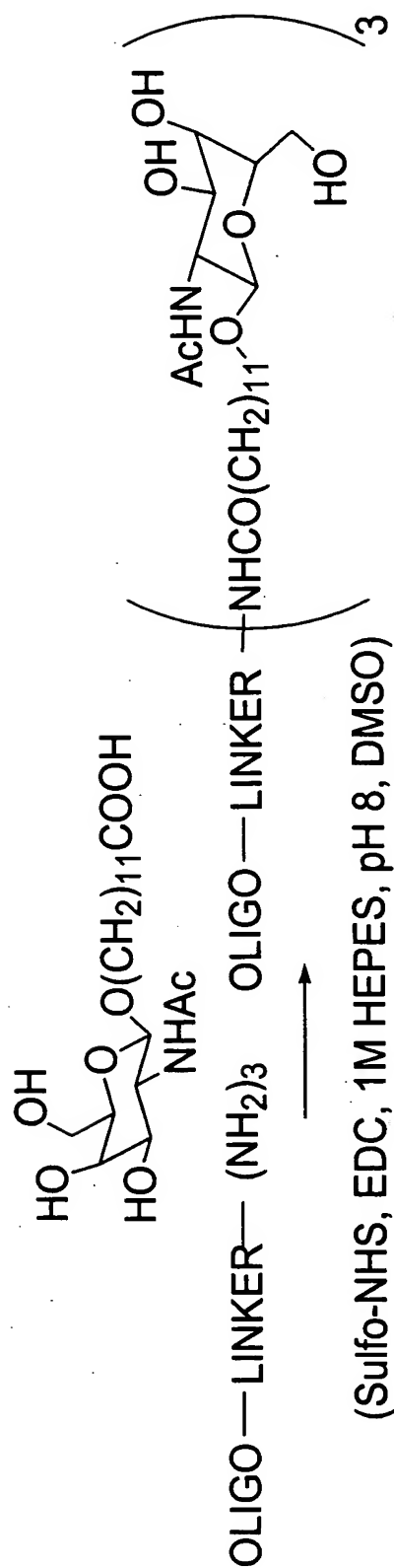
**Figure 21: 40-KDa PEG-Angiozyme vs Angiozyme**



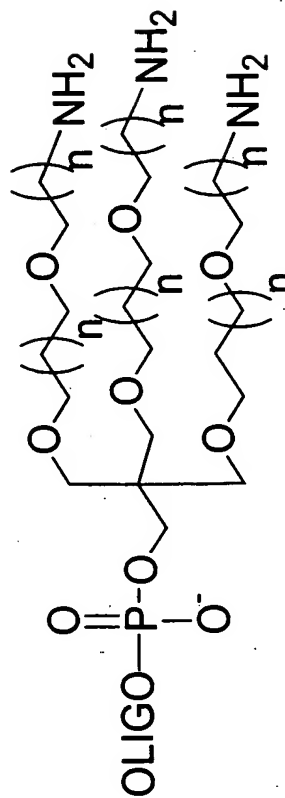
**Figure 22: Phospholipid-Angiozyme vs Angiozyme**



**Figure 23: Oligonucleotide-NAcGalactosamine post-synthetic coupling**



FOR EXAMPLE: OLIGO-LINKER =

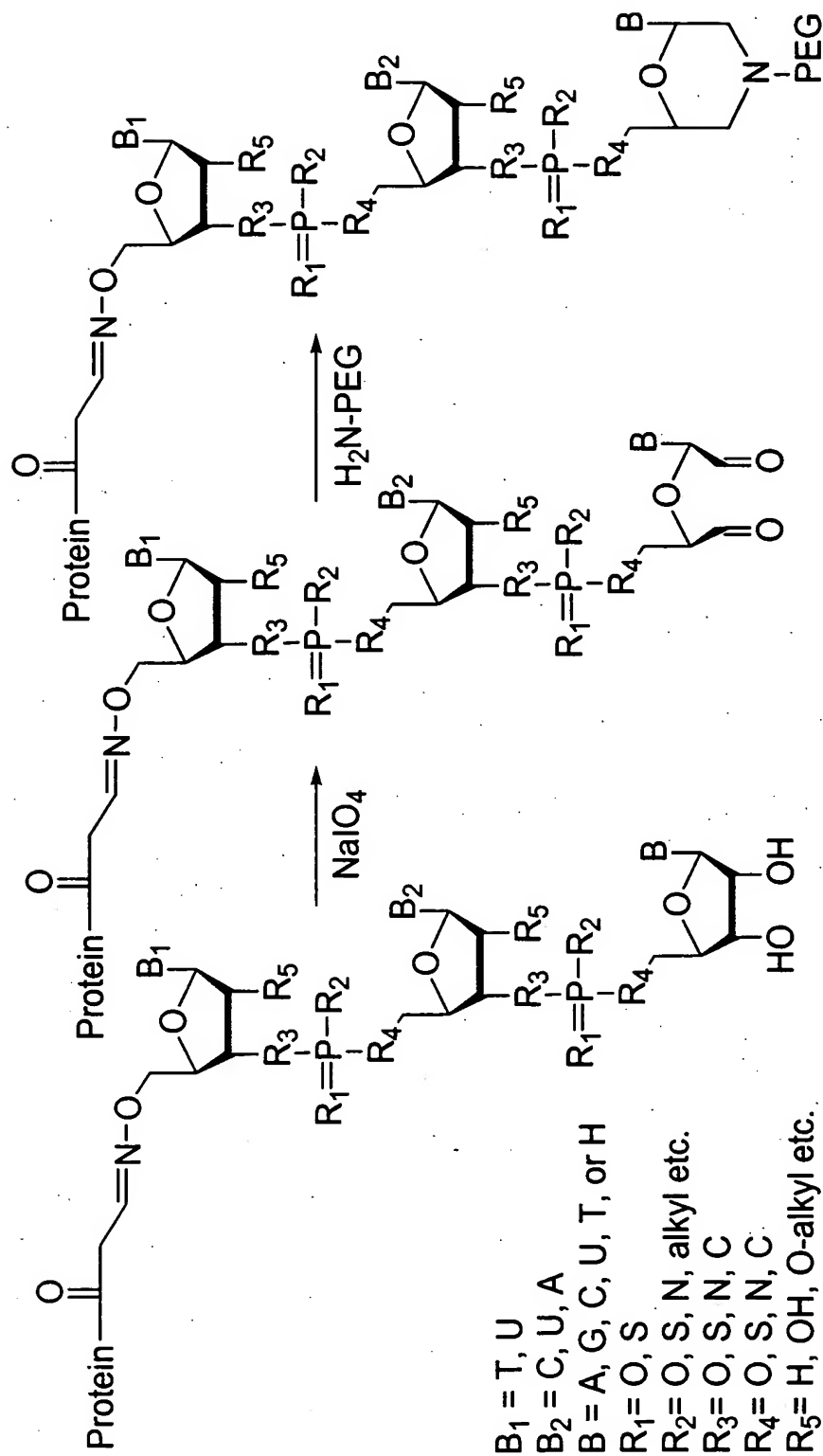


Where n is an integer from 1 to 20

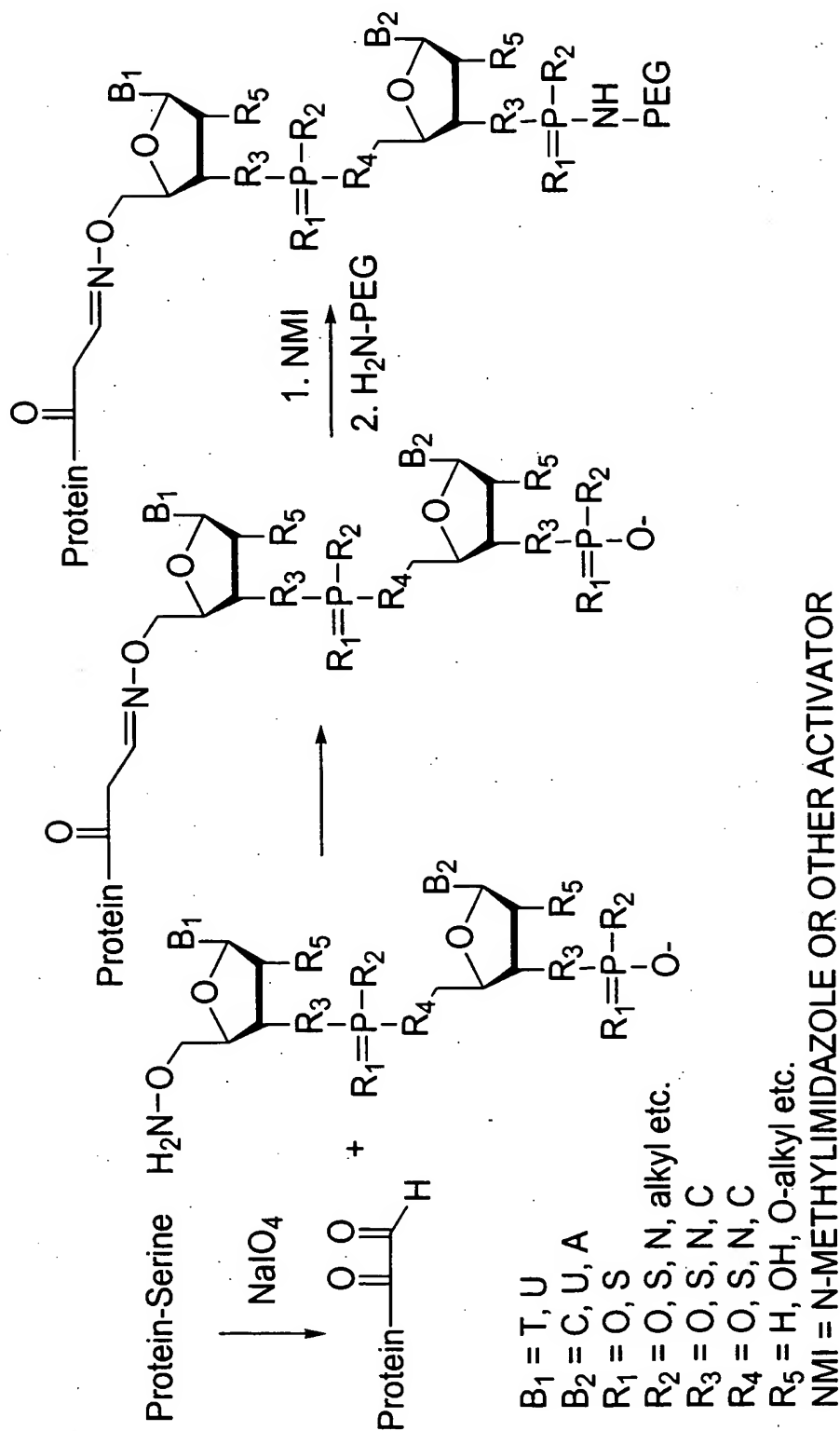




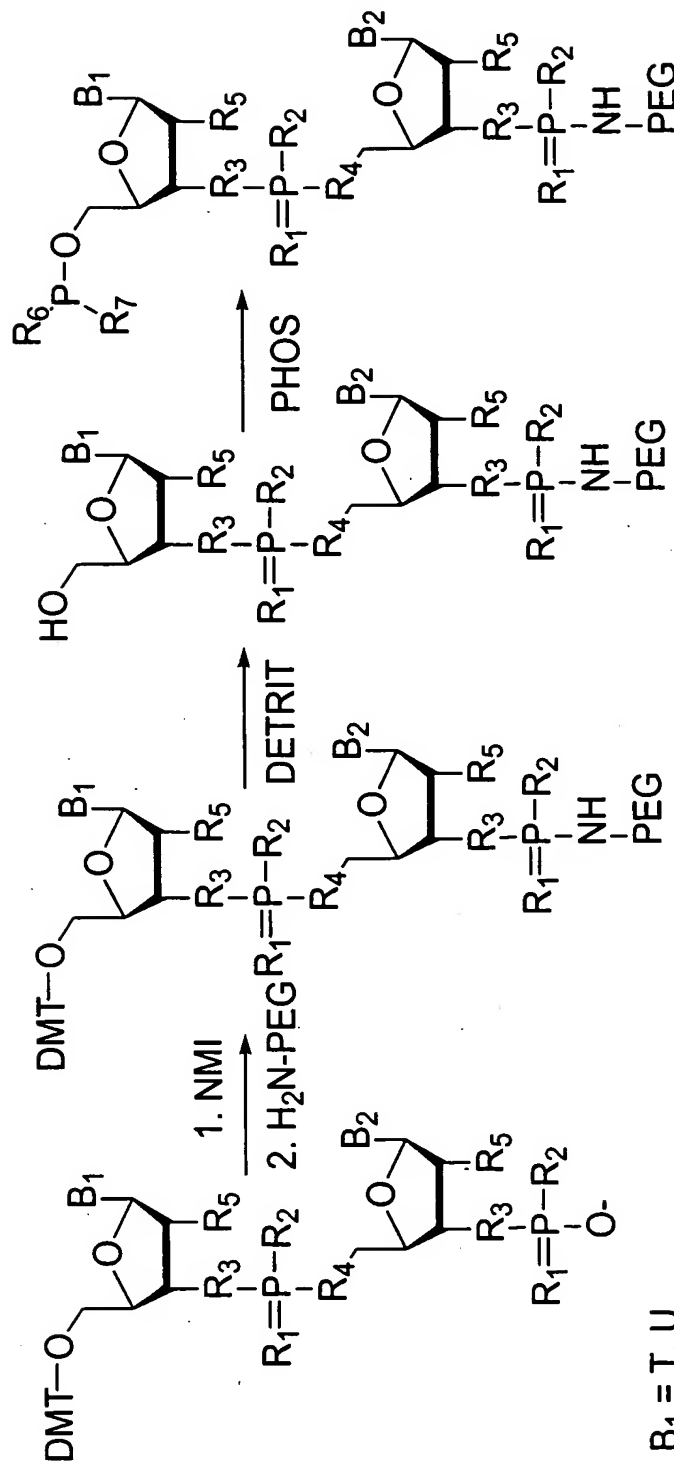
**Figure 24b: Protein cleavable linker PEG Conjugate**



**Figure 25: Protein PEG conjugate with cleavable linker**



**Figure 26a: PEG with cleavable linker**



B<sub>1</sub> = T, U

B<sub>2</sub> = C, U, A

R<sub>1</sub> = O, S

R<sub>2</sub> = O, S, N, alkyl etc.

R<sub>3</sub> = O, S, N, C

R<sub>4</sub> = O, S, N, C

R<sub>5</sub> = H, OH, O-alkyl etc.

R<sub>6</sub> = substituted nitrogen, eg. N(iPr)<sub>2</sub>

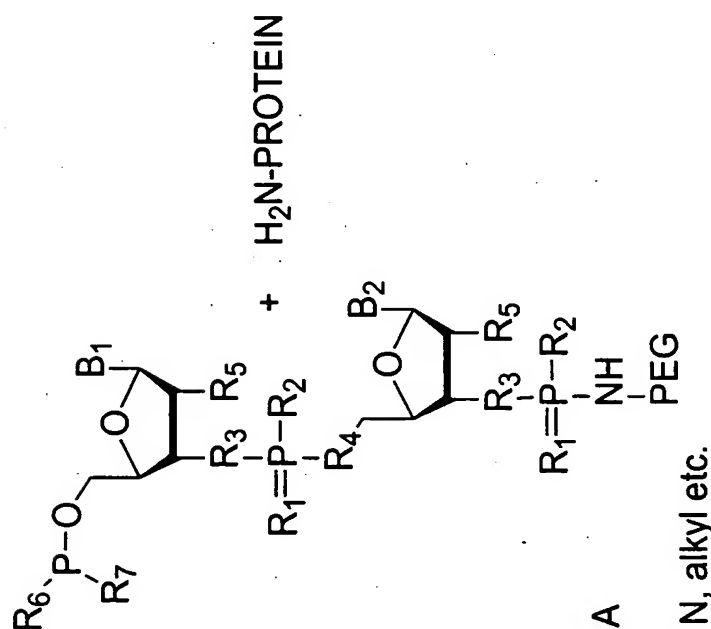
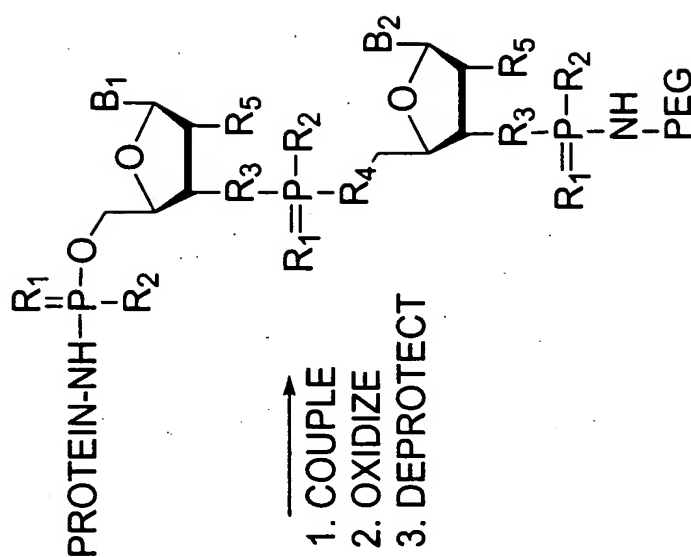
R<sub>7</sub> = O or S alkyl, cyanoalkyl, eg. cyanoethyl

PHOS = PHOSPHITYLATION

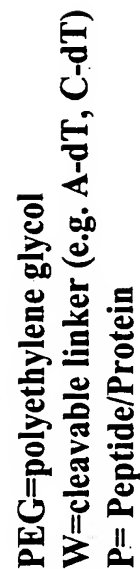
DETIT = DETRITYLATION

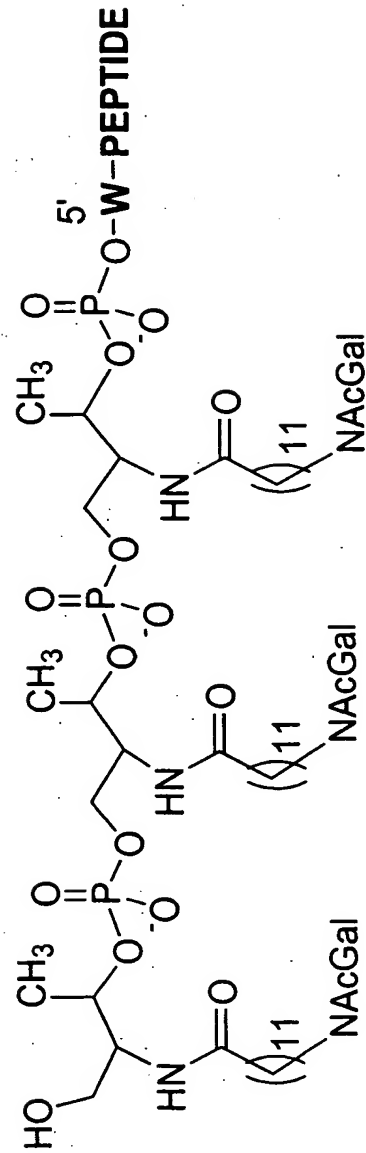
NMI = N-METHYLMIDAZOLE OR OTHER ACTIVATOR

**Figure 26b: Protein PEG conjugate with cleavable linker**



- $B_1 = \text{T, U}$   
 $B_2 = \text{C, U, A}$   
 $R_1 = \text{O, S}$   
 $R_2 = \text{O, S, N, alkyl etc.}$   
 $R_3 = \text{O, S, N, C}$   
 $R_4 = \text{O, S, N, C}$   
 $R_5 = \text{H, OH, O-alkyl etc.}$   
 $R_6 = \text{substituted nitrogen, eg. N(iPr)}_2$   
 $R_7 = \text{O or S alkyl, cyanoalkyl, eg. cyanoethyl}$

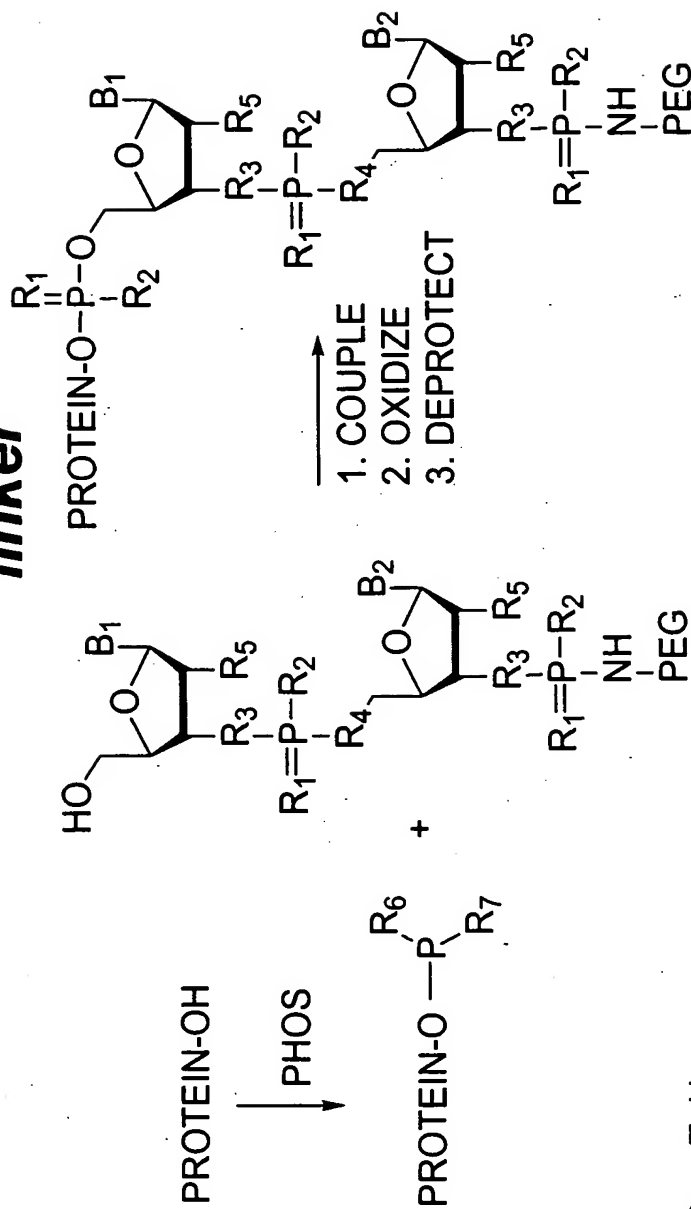




## N-acetyl-D-galactosamine conjugate

**W = cleavable linker (eg. A-dT, C-dT dimer)**

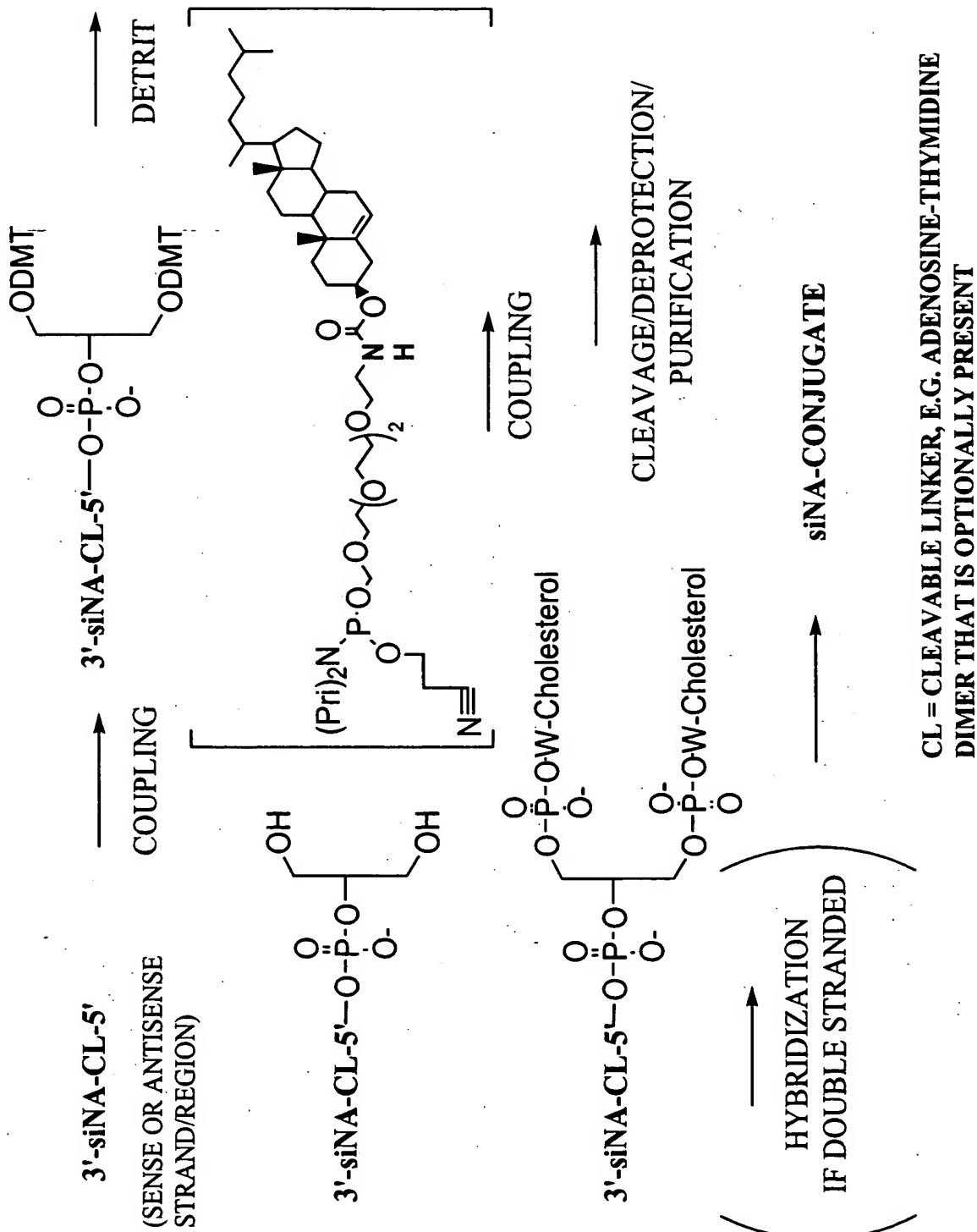
**Figure 29: Protein/PEG conjugate with cleavable linker**



B<sub>1</sub> = T, U  
 B<sub>2</sub> = C, U, A  
 R<sub>1</sub> = O, S  
 R<sub>2</sub> = O, S, N, alkyl etc.  
 R<sub>3</sub> = O, S, N, C  
 R<sub>4</sub> = O, S, N, C  
 R<sub>5</sub> = H, OH, O-alkyl etc.

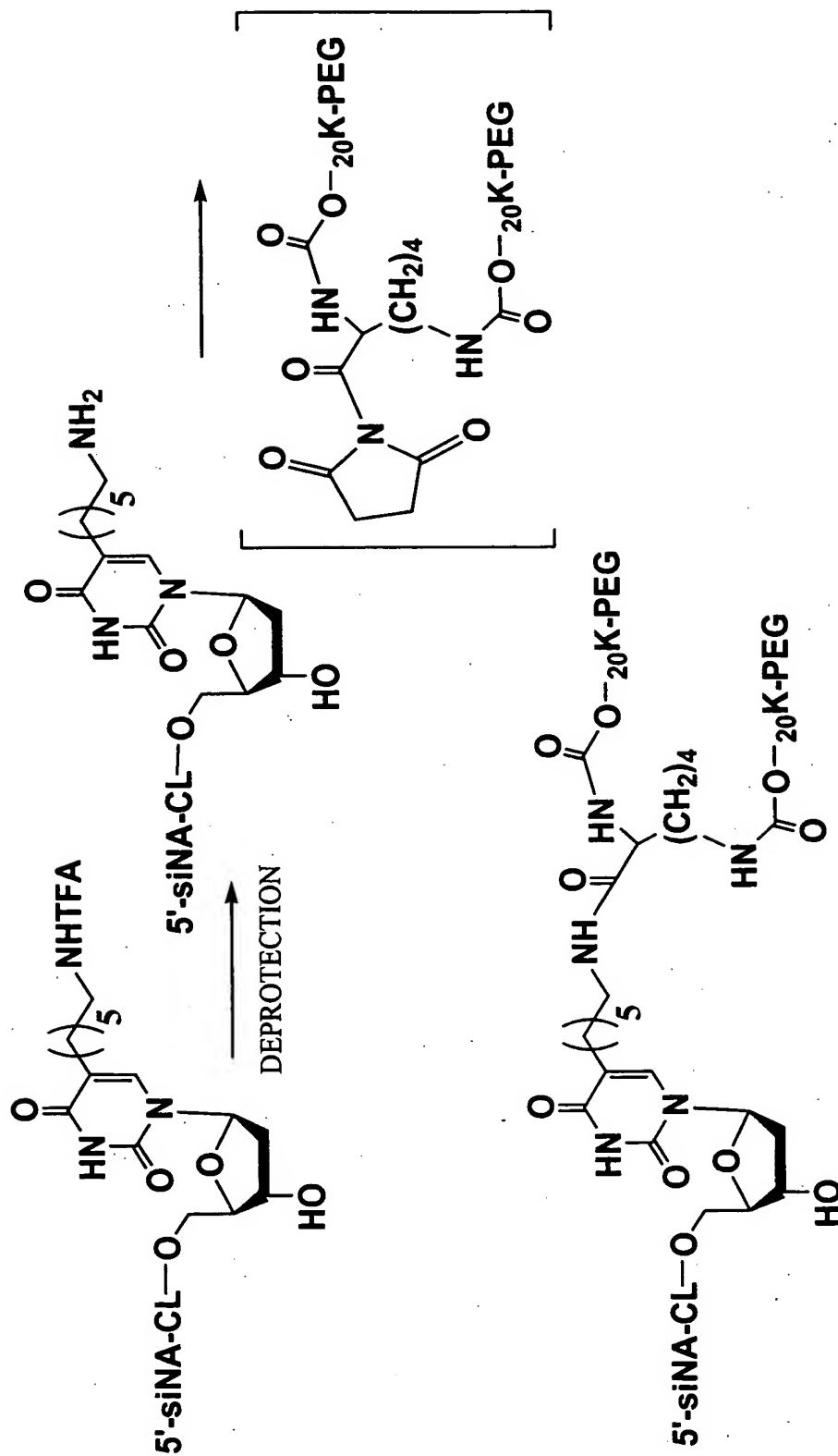
R<sub>6</sub> = substituted nitrogen, eg. N(iPr)<sub>2</sub>  
 R<sub>7</sub> = O or S alkyl, cyanoalkyl, eg. cyanoethyl  
 PHOS = PHOSPHITYLATION

**Figure 30: siNA Cholesterol Conjugate**



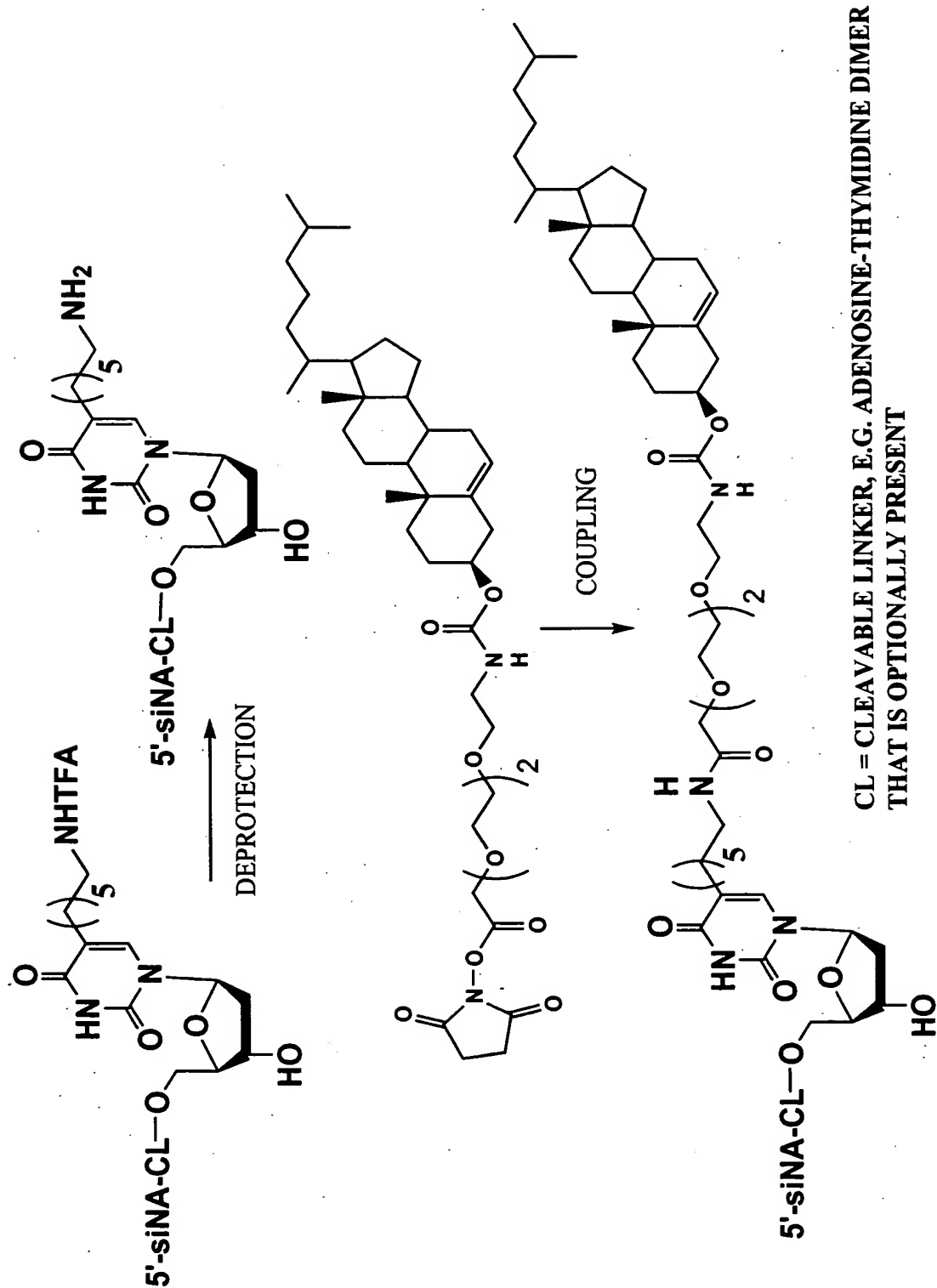


**Figure 31: siNA 3'-PEG Conjugate**

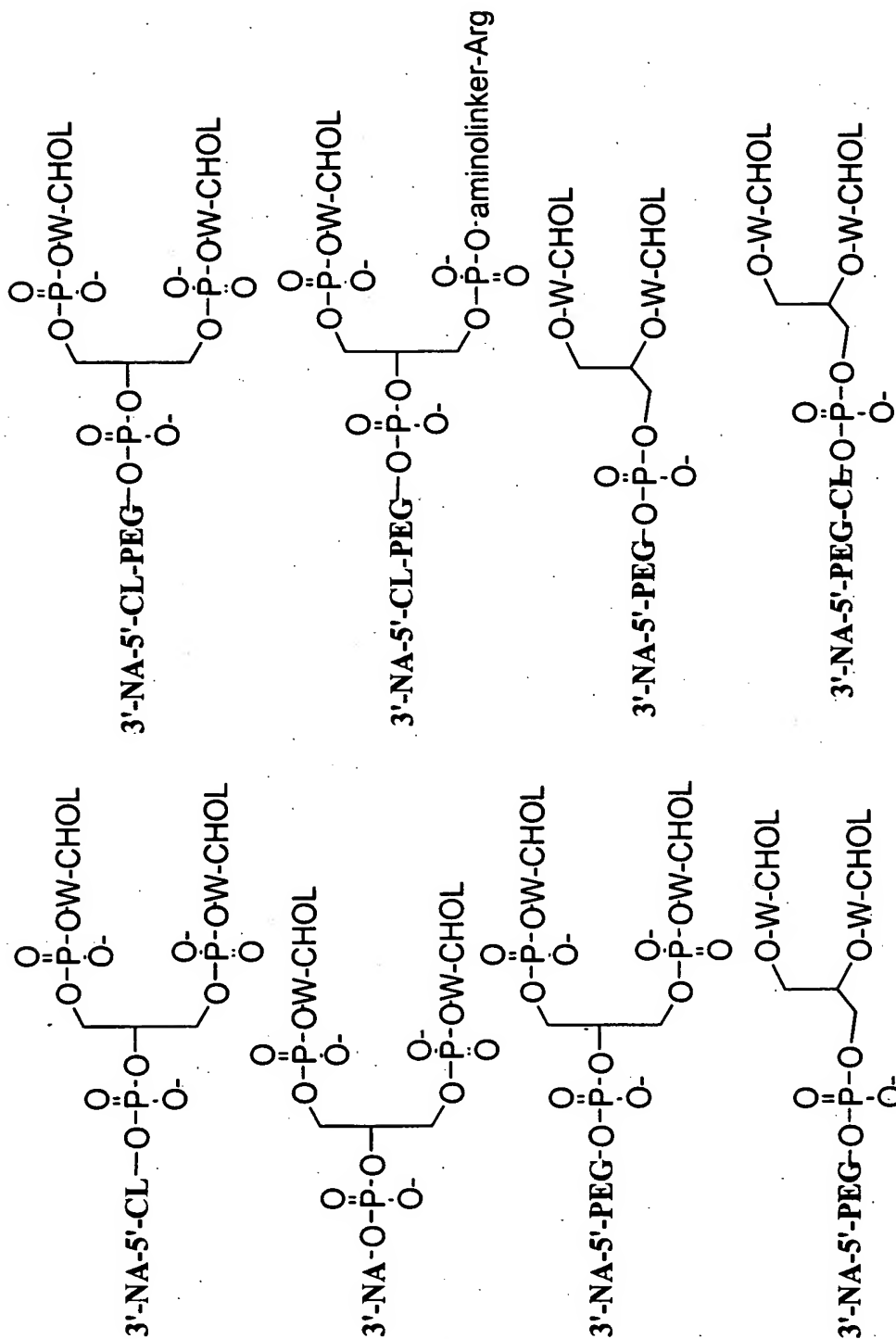


CL = CLEAVABLE LINKER, E.G. ADENOSINE-THYMIDINE DIMER  
 THAT IS OPTIONALLY PRESENT

**Figure 32: siNA 3'-Cholesterol Conjugate**



**Figure 33: Nucleic Acid Cholesterol Conjugates**



PEG=polyethylene glycol

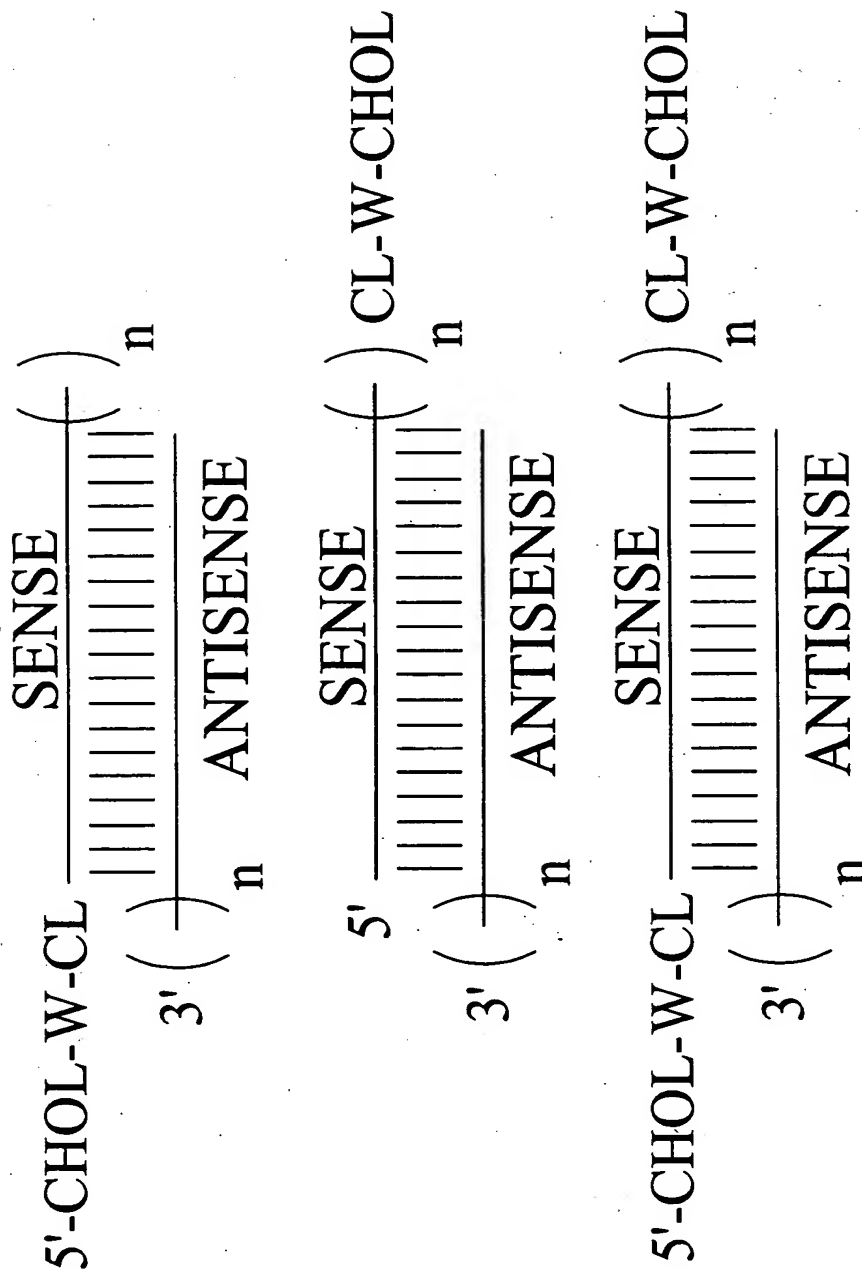
CL=cleavable linker (e.g. A-dT, C-dT)

NA= Nucleic Acid Molecule such as siNA, antisense, or enzymatic nucleic acid

CHOL=cholesterol or an analog or metabolite thereof

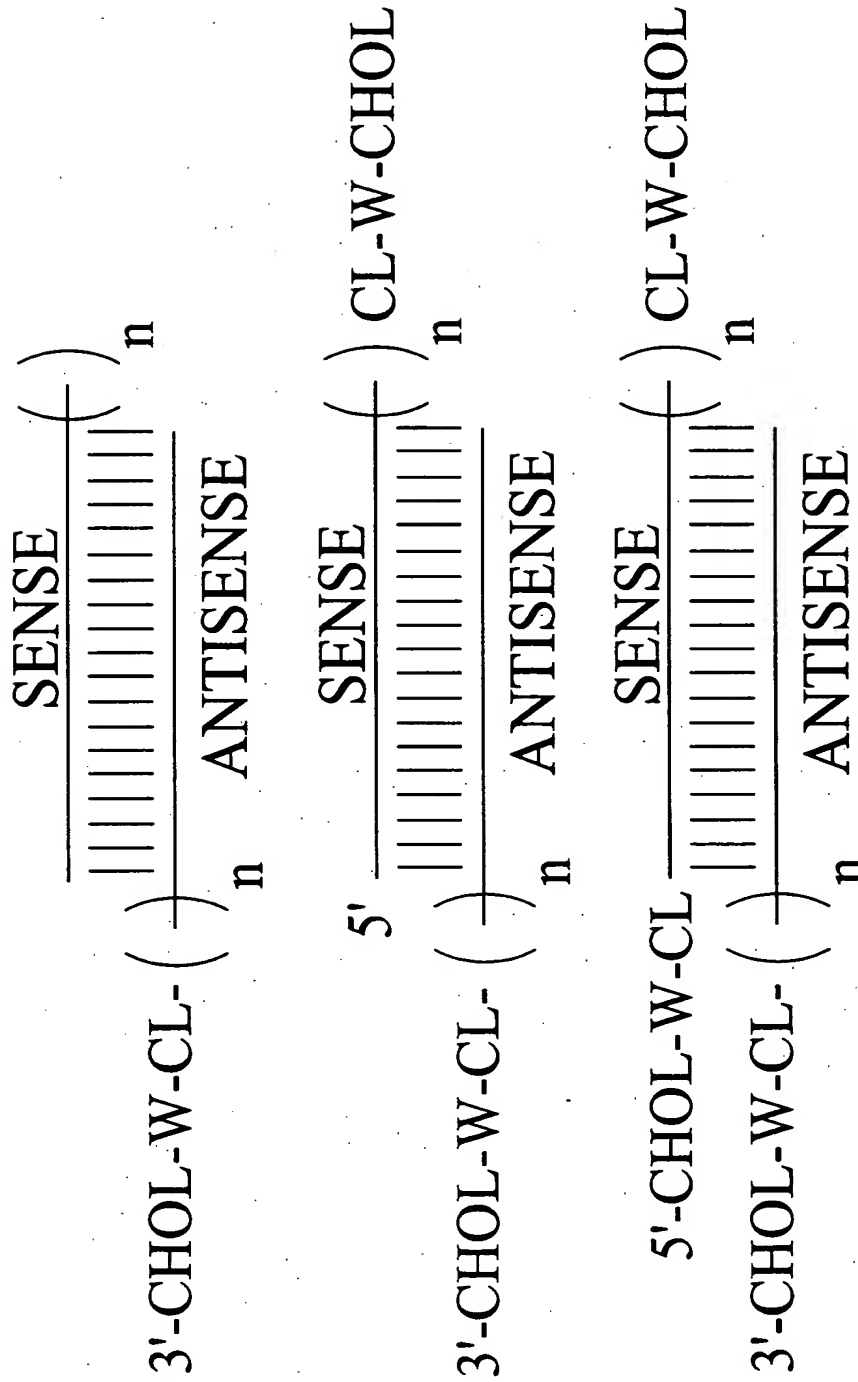
W= linker molecule (see for example Formulae 109 or 112)

**Figure 34: siNA Cholesterol Conjugates**



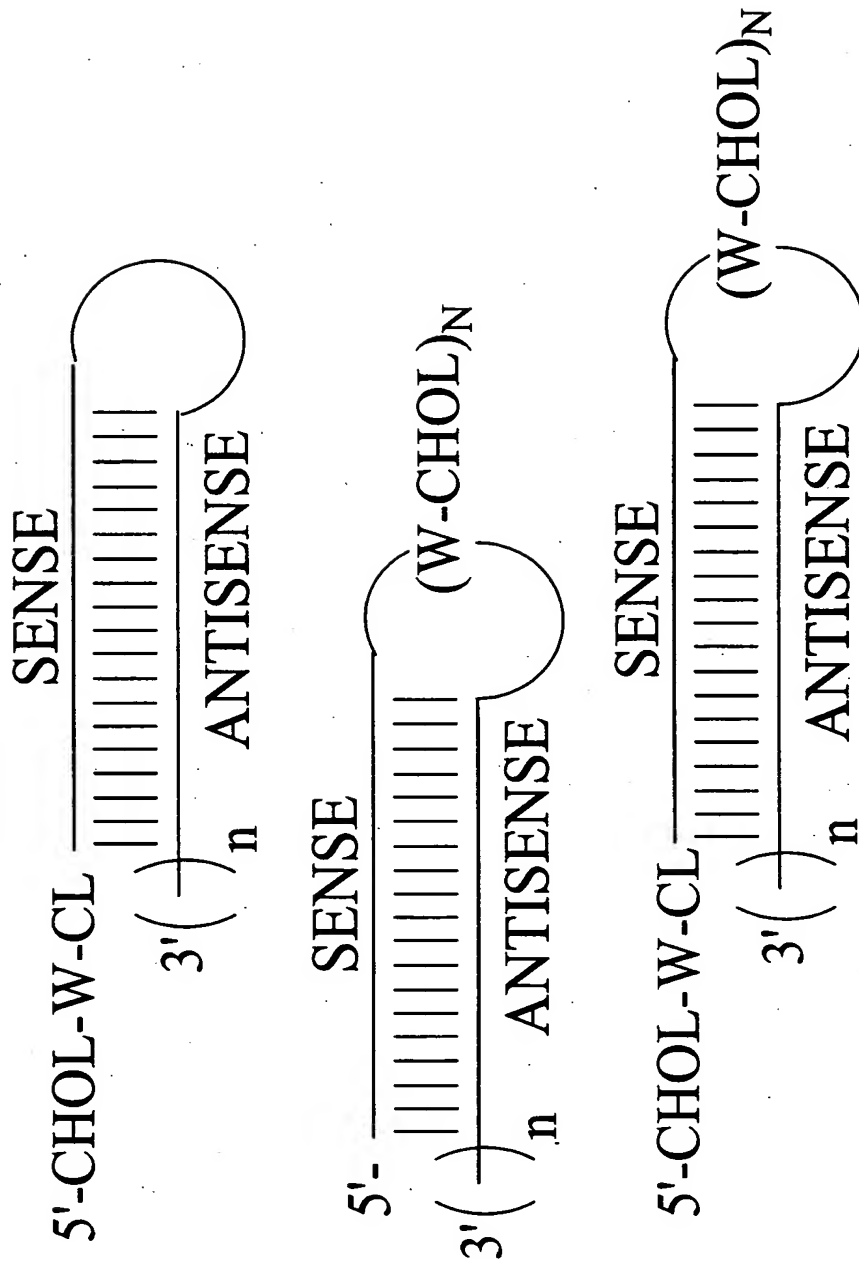
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
 CHOL=cholesterol or an analog or metabolite thereof  
 W= linker molecule (see for example Formulae 107, 108, 109 or 115)  
 n = integer, e.g. 1, 2, or 3

**Figure 35: siNA Cholesterol Conjugates**



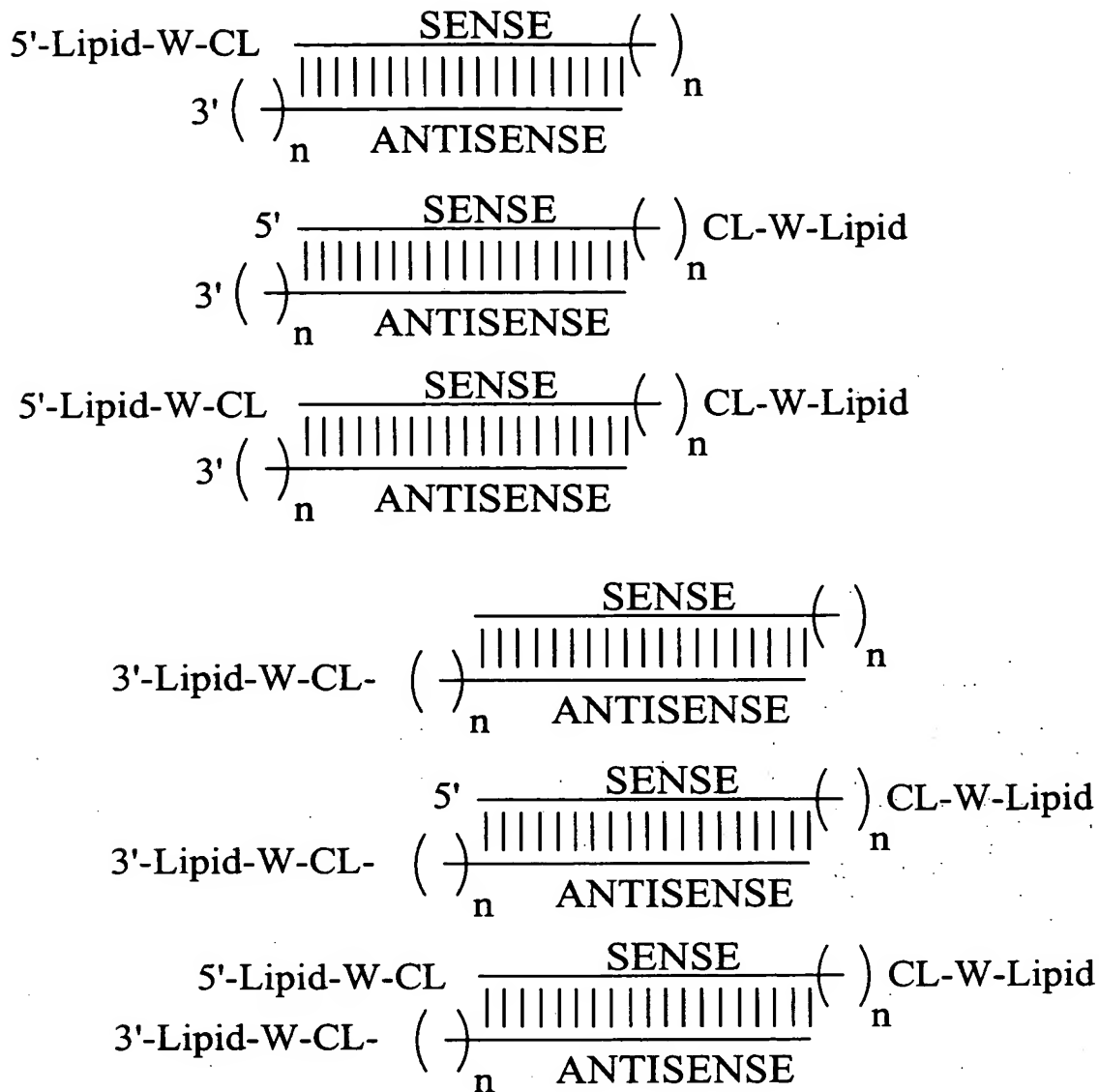
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
 CHOL=cholesterol or an analog or metabolite thereof  
 W= linker molecule (see for example Formulae 107, 108, 109 or 115)  
 n = integer, e.g. 1, 2, or 3

**Figure 36: siNA Cholesterol Conjugates**



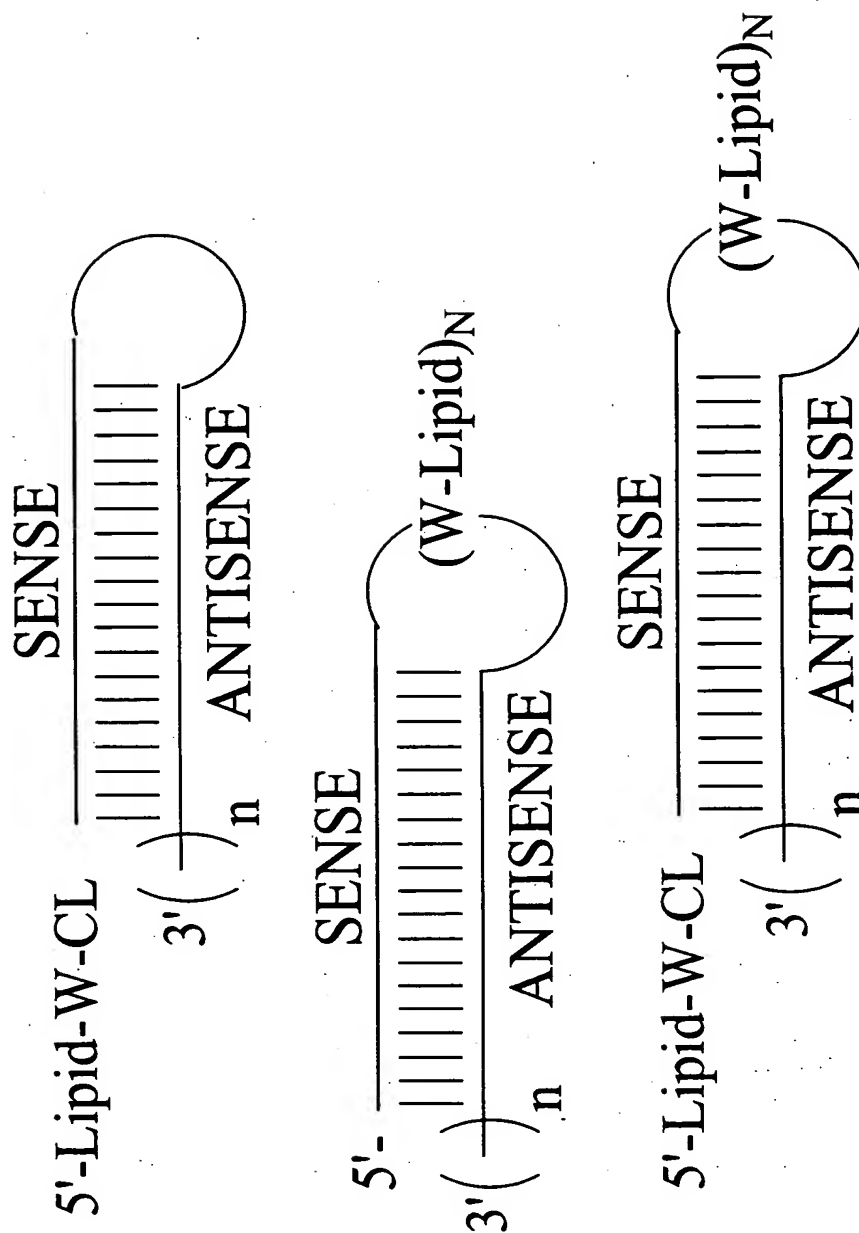
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
 CHOL=cholesterol or an analog or metabolite thereof  
 W= linker molecule (see for example Formulae 107, 108, 109 or 112)  
 $n$  = integer, e.g. 1, 2, or 3  
 $N$ =integer, e.g. 1, 2, 3, or 4

## Figure 37: siNA Lipid Conjugates



**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**  
**Lipid=Straight chain or branched alkyl or fatty acid, e.g. C<sub>18</sub>H<sub>37</sub>**  
**W= linker molecule (see for example Formulae 48, 49, 64, or 65)**  
**n = integer, e.g. 1, 2, or 3**

**Figure 38: siNA Lipid Conjugates**



**CL**=cleavable linker (e.g. A-dT, C-dT) that is optionally present

**Lipid**=Straight chain or branched alkyl or fatty acid, e.g.  $\text{C}_{18}\text{H}_{37}$

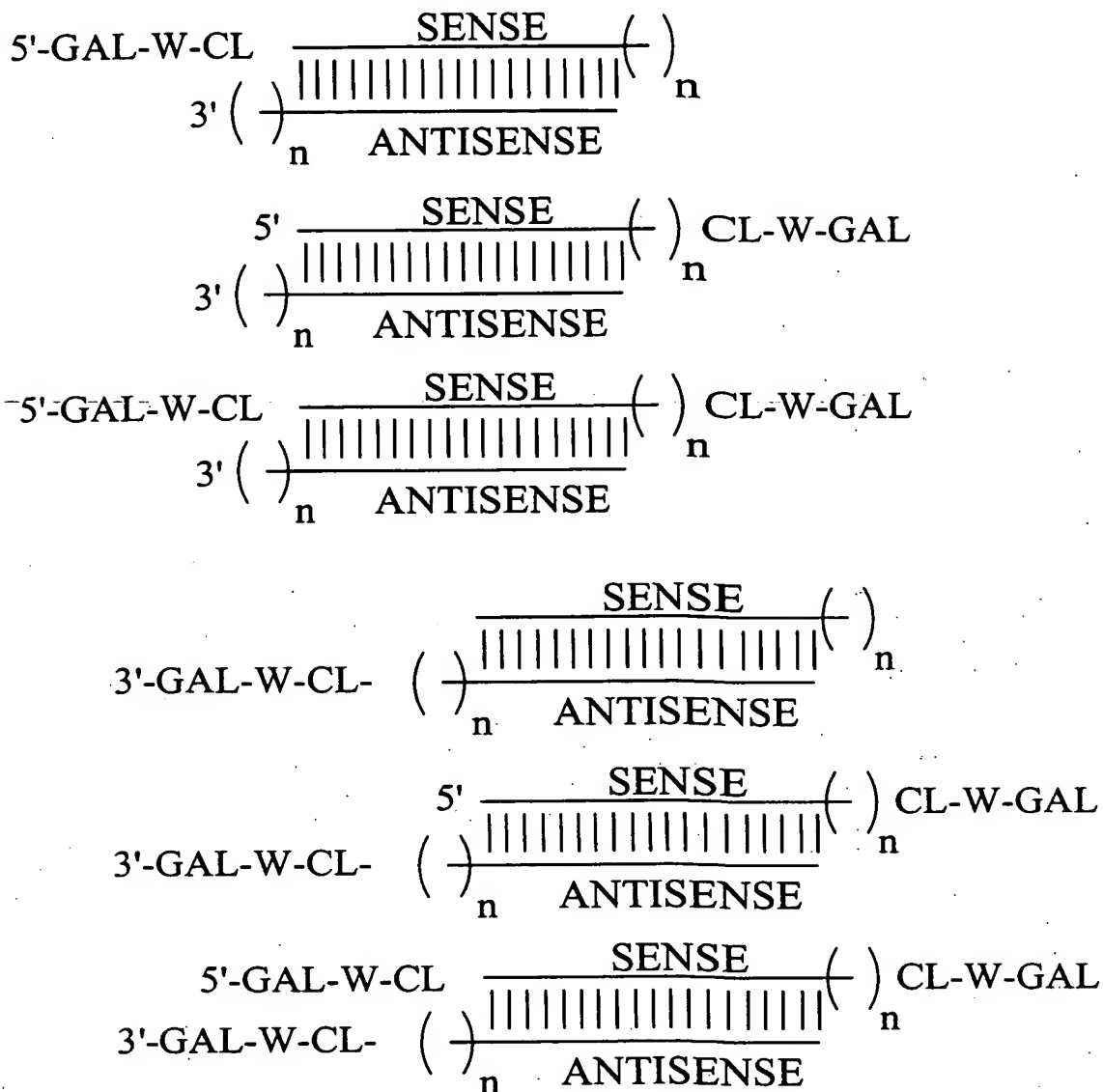
**W**= linker molecule (see for example Formulae 48, 49, 64, or 65)

**n** = integer, e.g. 1, 2, or 3

**N**=integer, e.g. 1, 2, 3, or 4



**Figure 39: siNA Galactosamine Conjugates**



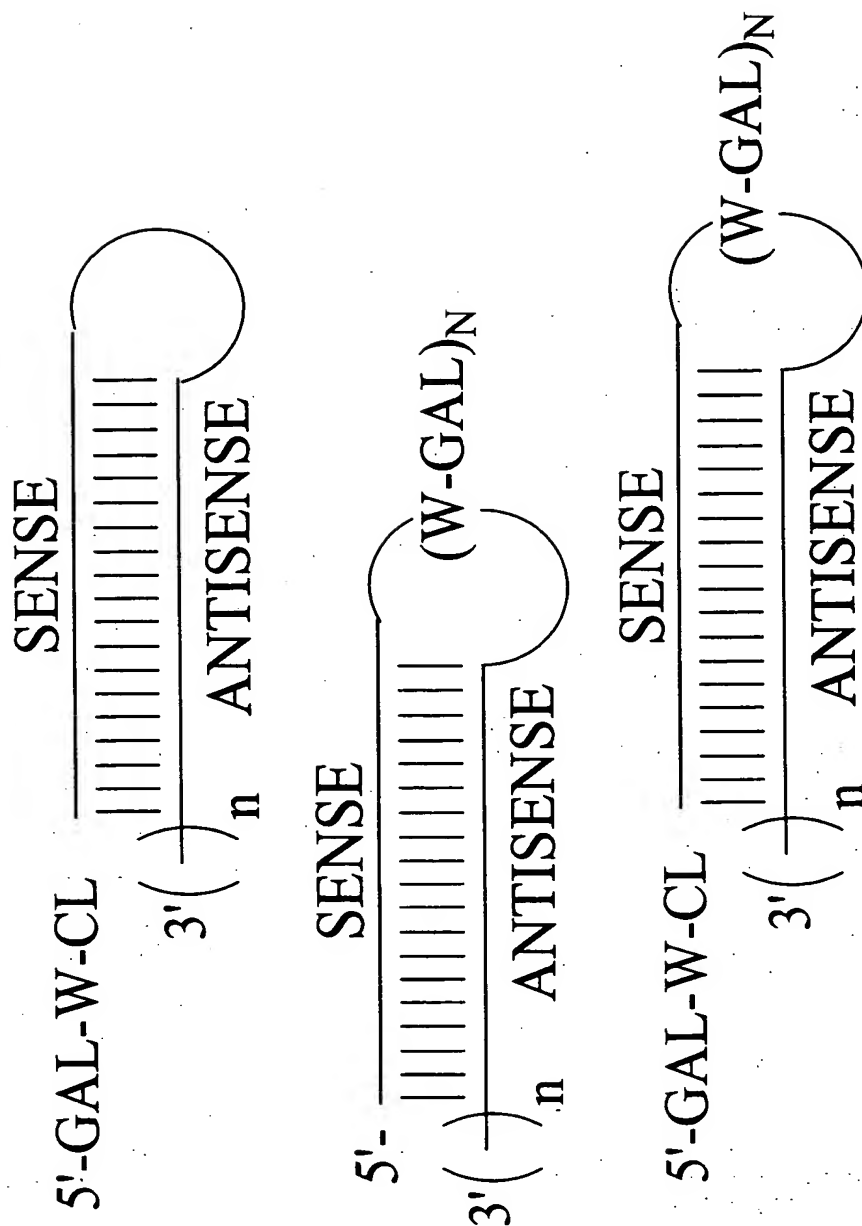
**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**

**GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106**

**W= linker molecule (see for example Formulae 102 or 103)**

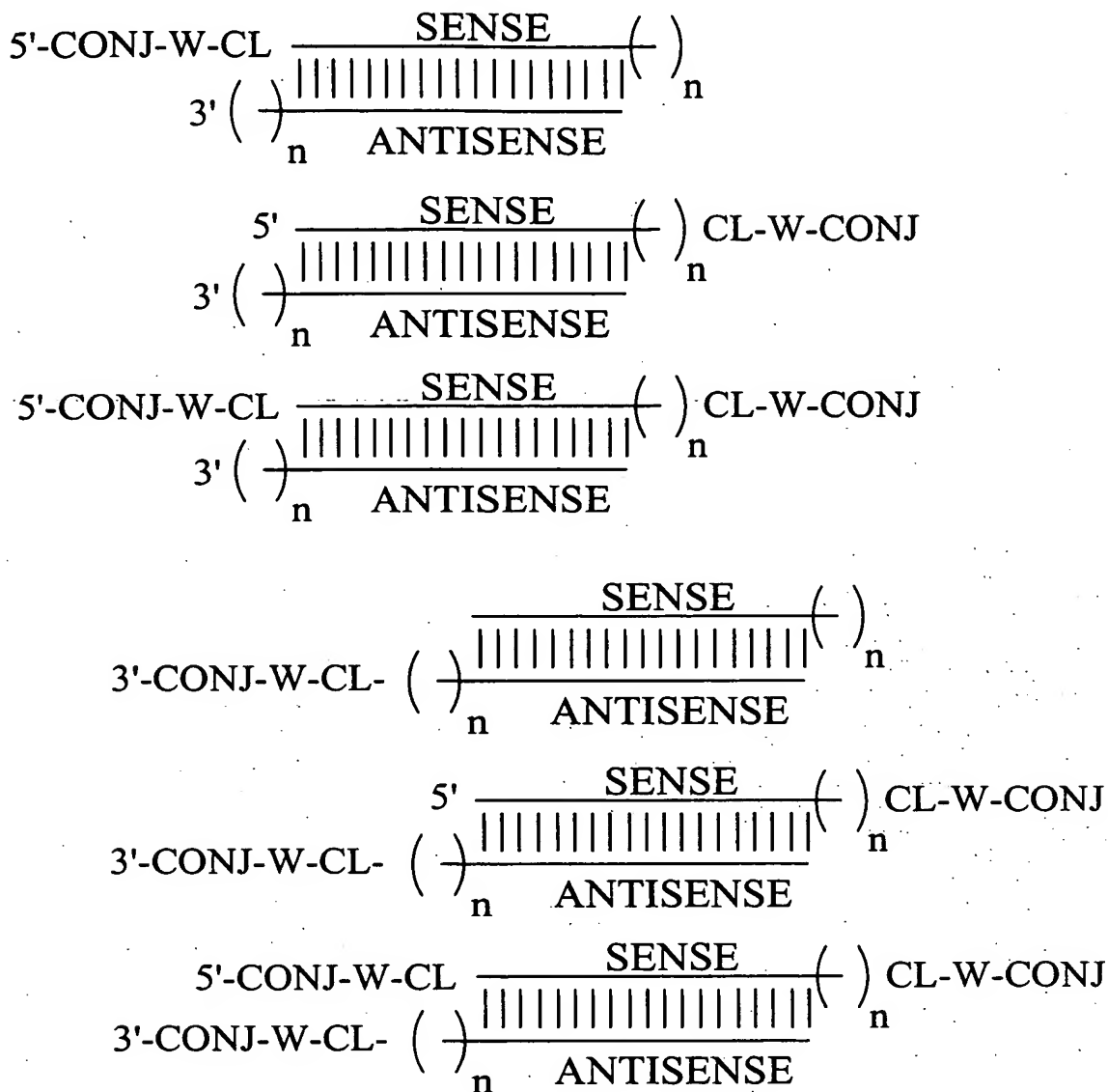
**n = integer, e.g. 1, 2, or 3**

**Figure 40: siNA Galactosamine Conjugates**



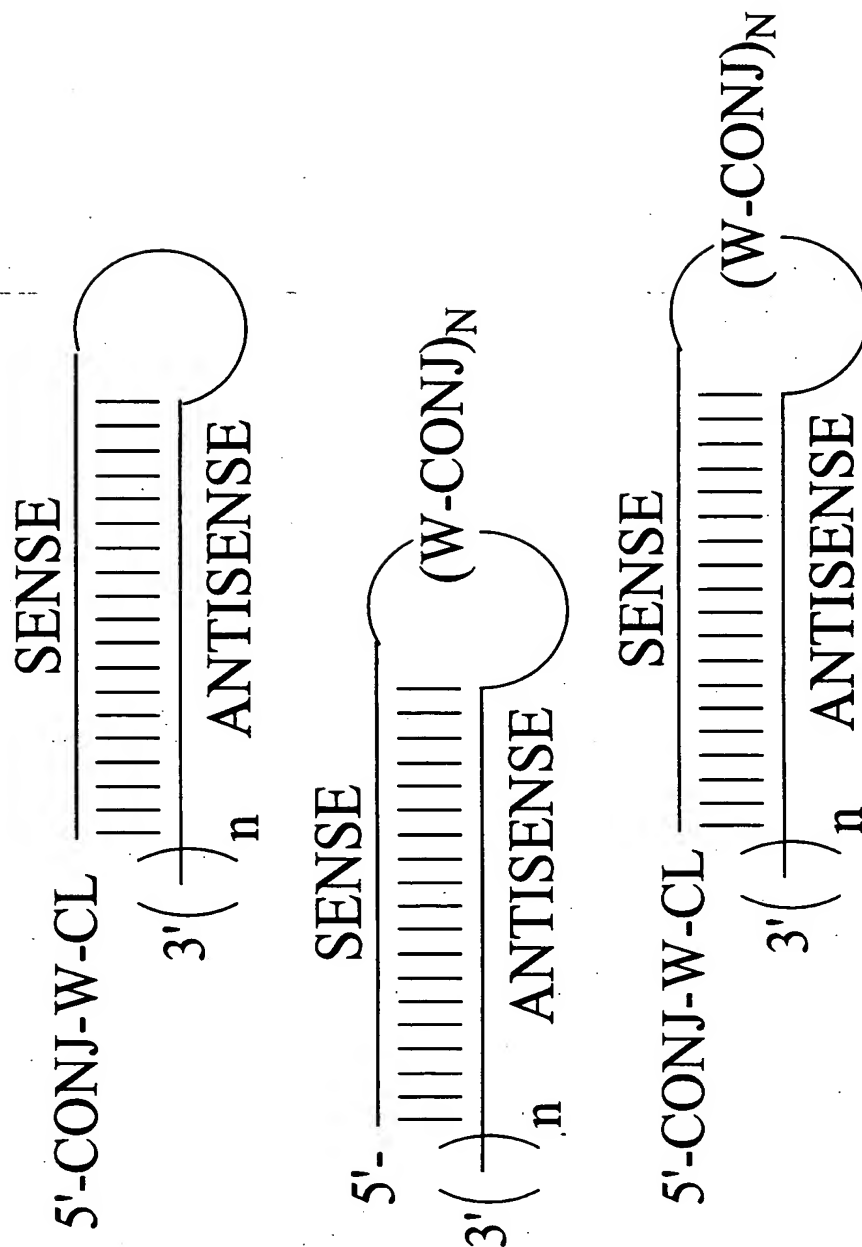
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
 GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106  
 W= linker molecule (see for example Formulae 102 or 103)  
 n = integer, e.g. 1, 2, or 3  
 N=integer, e.g. 1, 2, 3, or 4

**Figure 41: Generalized siNA Conjugate Design**



CONJ=any biologically active molecule or conjugate as described herein  
 CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present  
 W= linker molecule  
 n = integer, e.g. 1, 2, or 3

**Figure 42: Generalized siNA Conjugate design**



CONJ=any biologically active molecule or conjugate as described herein

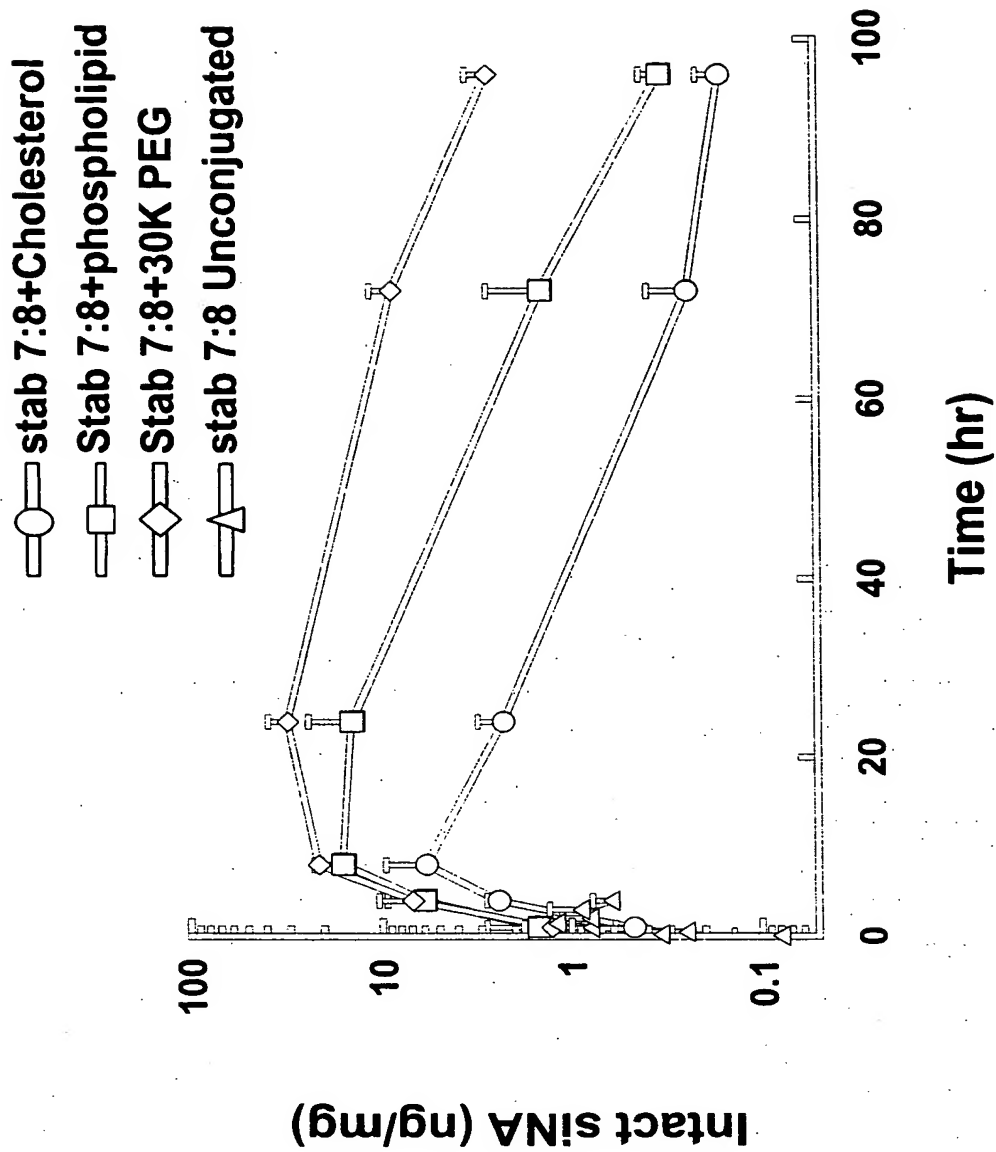
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present

W= linker molecule

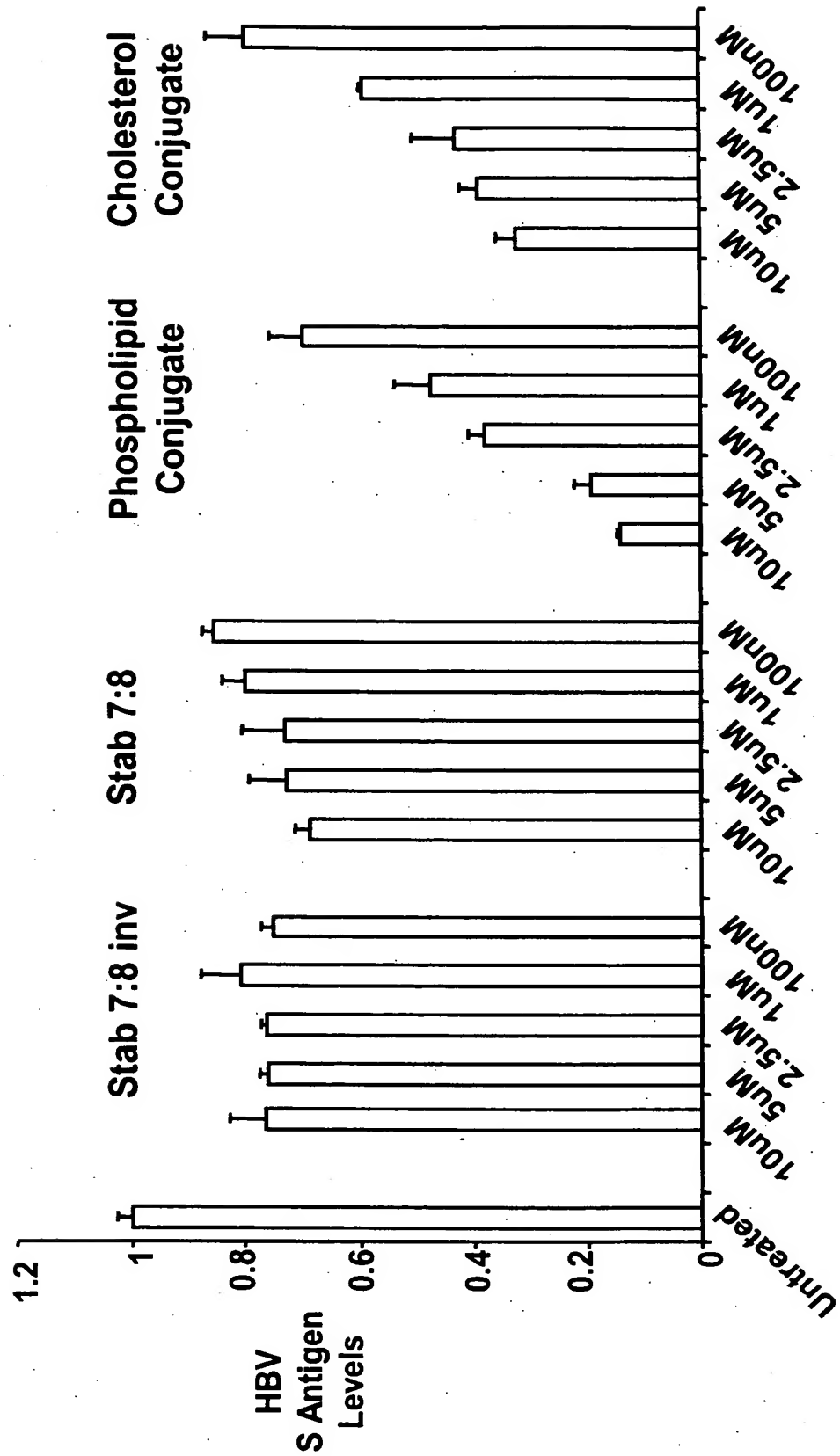
n = integer, e.g. 1, 2, or 3

N=integer, e.g. 1, 2, 3, or 4

**Figure 43: Distribution of Intact siNA in Liver After SC Administration of Conjugated or Unconjugated Chemistries**

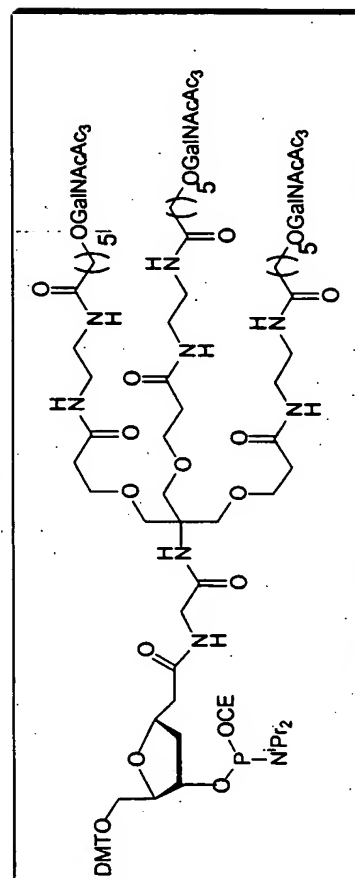
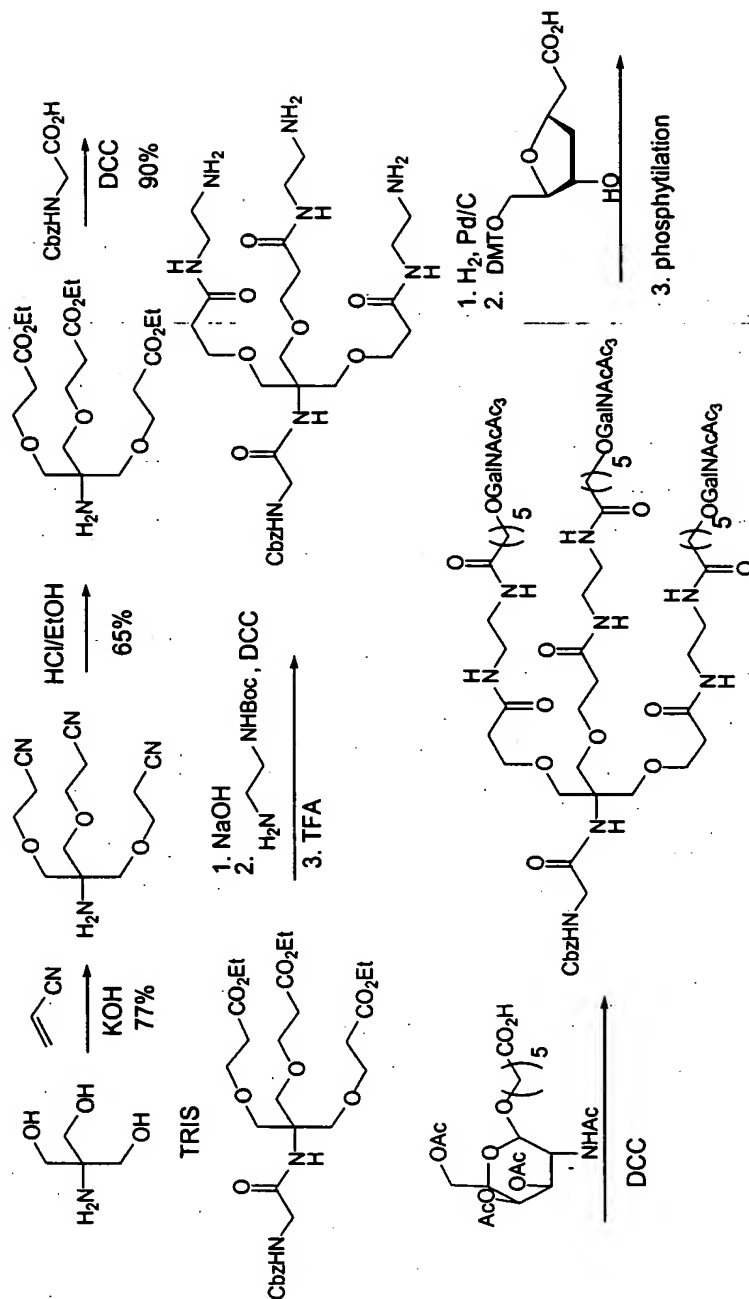


**Figure 44: Lipid Free Delivery of HBV siNA Conjugates in Cell Culture**



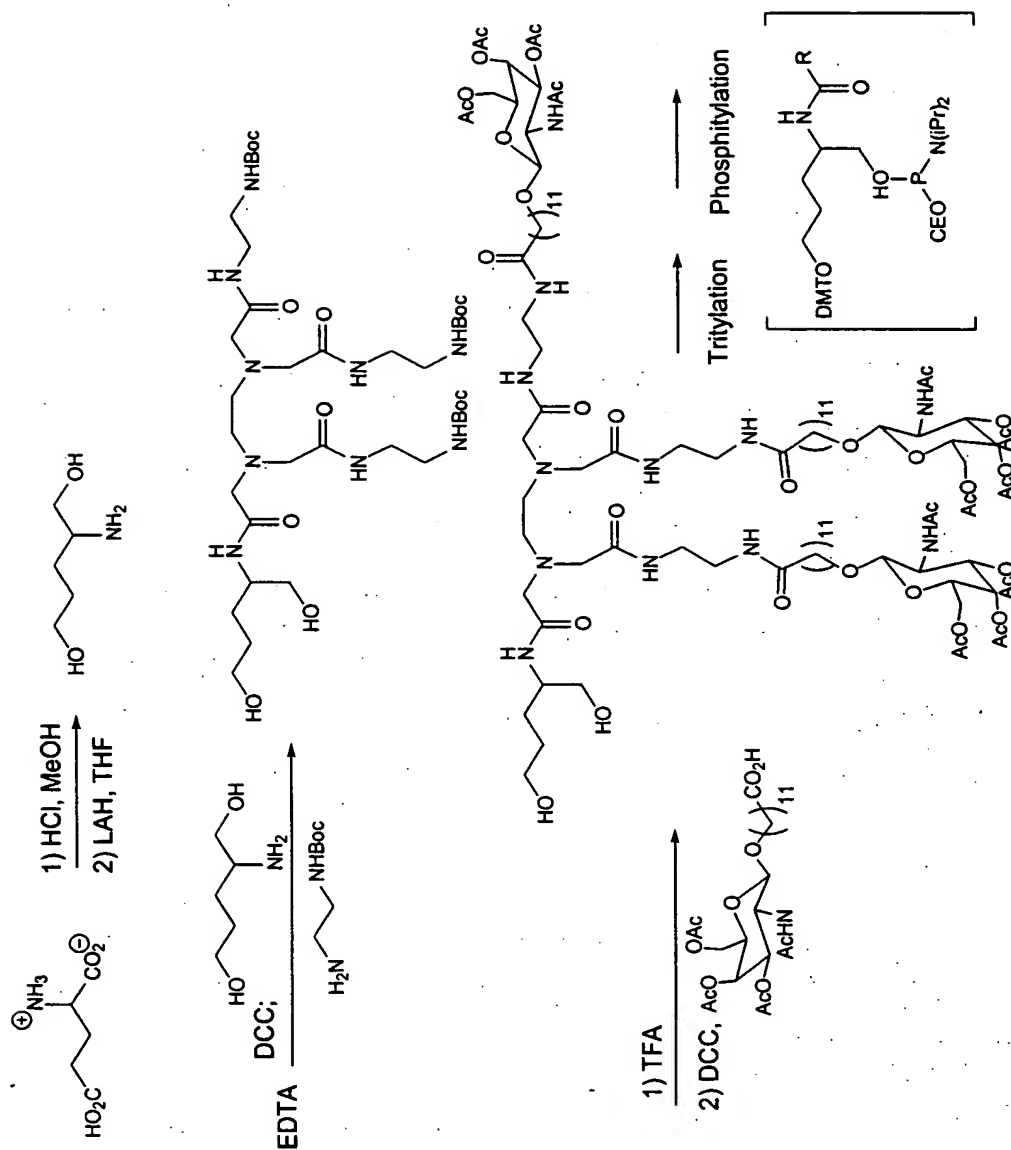


**Figure 46: Synthesis of "tri" Galactosamine phosphoramidite**

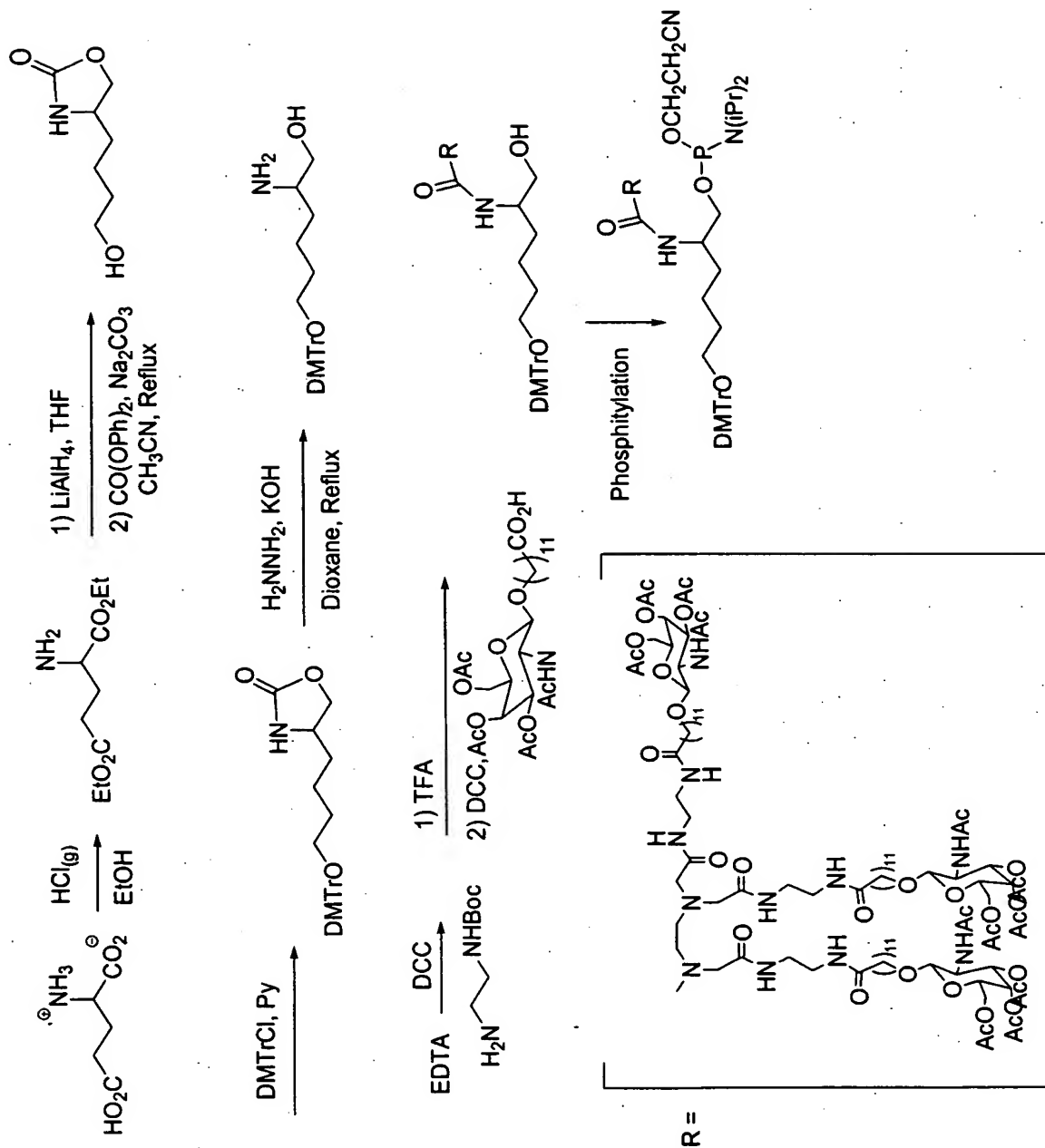




**Figure 47: Synthesis of another Tri-Galactosamine Conjugate**



**Figure 48: Alternate Synthesis of Tri-Galactosamine Conjugate**



**Figure 49: Synthesis of NHS Cholesterol Conjugate**

